VOL. 36 NOVEMBER 1960 NO. 11

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

FRANCIS O. SCHMITT

PHILIP LEVINE

H. D. KRUSE

LAURENCE FARMER

NEW YORK PATHOLOGICAL SOCIETY

NEW YORK HEART ASSOCIATION

for immed[illegible] asthma relief

and 22½% more vital capacity

Medihaler®

[illegible] aerosol administration

[illegible] maximal con[illegible]
[illegible]ne or on-

Available with either of the two outstanding bronchodilators

Medihaler-EPI®

Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each automatically measured dose contains 0.15 mg. epinephrine.

Medihaler-ISO®

Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each automatically measured dose contains 0.075 mg. isoproterenol.

Optimal effect from Minimal Dosage

Riker

Northridge, California

safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.[1-3] *Figure #1* graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.[3]

"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in *figure #2*, the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,[4] and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.[5]

In *figure #3*, the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

'Clarin', which is heparin in the form of a *sublingual tablet*, has been demonstrated to clear lipemic serum.[2,6,7] Furthermore, a two-year study using matched controls resulted in a statistically significant reduction of recurrent myocardial infarction in 130 patients treated with 'Clarin'.[8]

'Clarin' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

References: **1.** Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. **2.** Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. *7*:225 (Apr.) 1959. **3.** Stutman, L. J., and George, M.: Clin. Res. *7*:225 (Apr.) 1959. **4.** Wilkinson, C. F., Jr.: Annals of Int. Med. *45*:674 (Oct.) 1956. **5.** Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. *163*:727 (March 2) 1957. **6.** Fuller, H. L.: Angiology 9:311 (Oct.) 1958. **7.** Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959. **8.** Fuller, H. L.: Circulation *20*:699 (Oct.) 1959.

Clarin*

(sublingual heparin potassium, Leeming)

Fig. 1

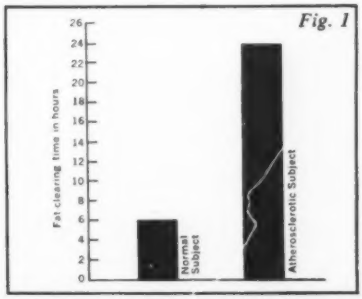


Fig. 2

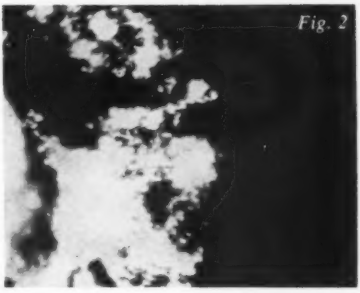
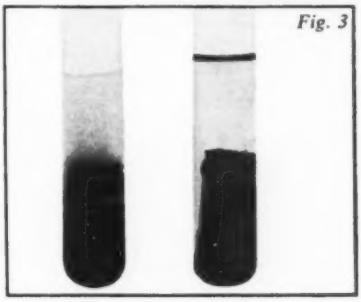


Fig. 3



Indication: For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: 'Clarin' is supplied in bottles of 50 pink, sublingual tablets, each containing 1500 I.U. of heparin potassium.

*Registered trade mark. Patent applied for.

Thos. Leeming & Co., Inc.
New York 17, N. Y.

Your surgical convalescent feels better because he is better with

Durabolin®

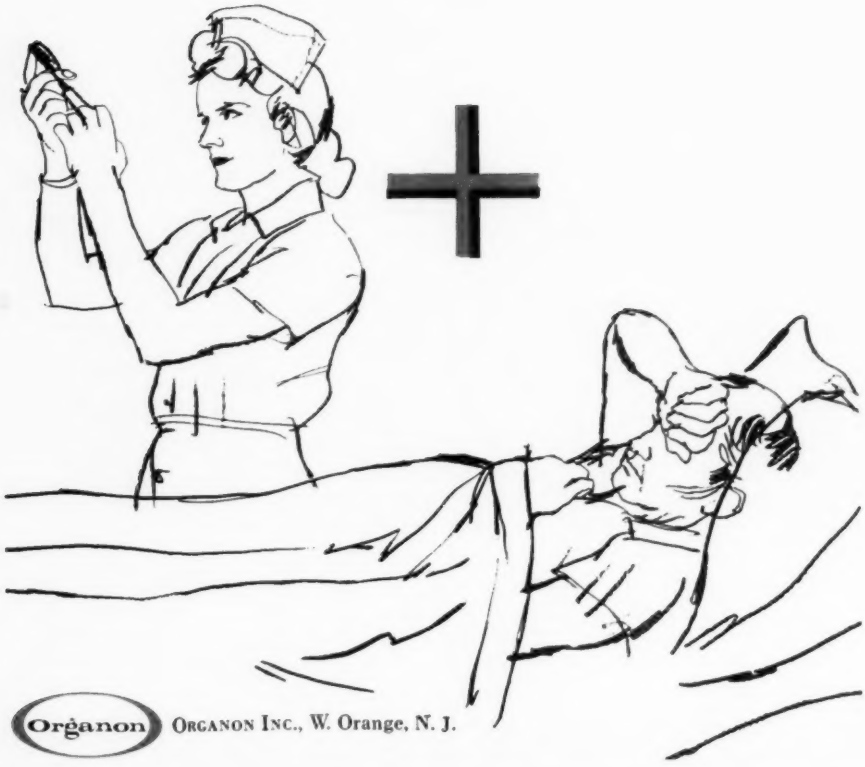
(Nandrolone phenpropionate injection, ORGANON)

1 cc. once each week

for safe potent anabolic stimulation

+ to maintain positive nitrogen balance
+ to promote rapid wound healing
+ to restore appetite, strength, vitality
+ to shorten convalescence, save nursing time
+ to reduce the cost of recovery

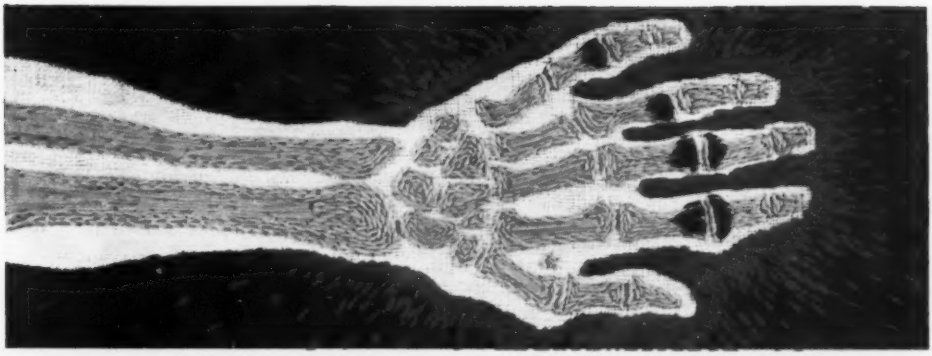
Supplied: 1-cc. ampuls (box of three) and 5-cc. vials, 25 mg. nandrolone phenpropionate/cc.
Adults: 1 cc. i.m. each week, or 2 cc. every other week.

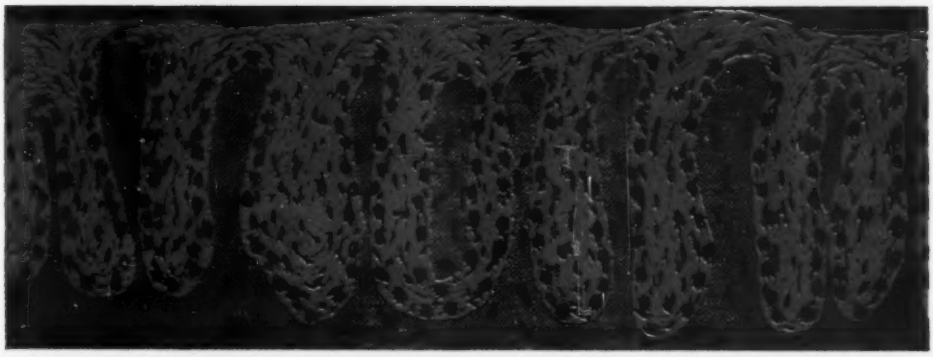


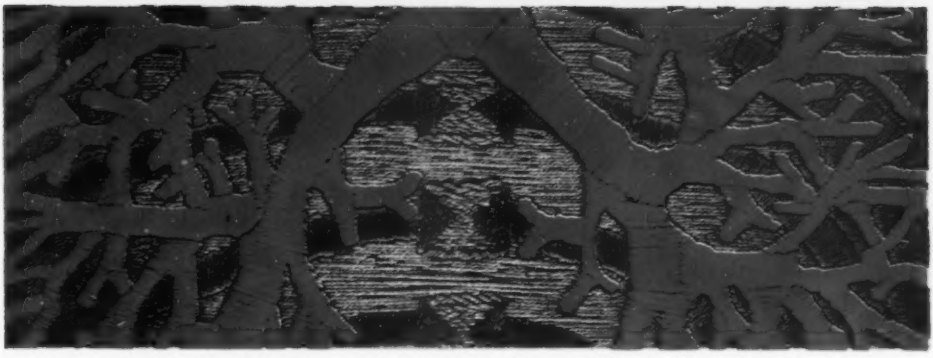
Organon ORGANON INC., W. Orange, N. J.

The Bulletin of The New York Academy of Medicine, Vol. 36, No. 11, November, 1960. Published Monthly by The New York Academy of Medicine, 2 East 103 Street, New York 29, N. Y. Entered as second-class matter February 3, 1928, at the Post Office at New York, N. Y., under the act of August 24, 1912. Postage paid at New York, N. Y. Annual subscription United States and Canada $8.00. All other countries $9.00. Single copies 90c.

a promise fulfilled







All corticosteroids provide symptomatic control in rheumatoid arthritis, inflammatory dermatoses, and bronchial asthma. They *differ* in the frequency and severity of side effects. Introduced in 1958, ARISTOCORT Triamcinolone bore the promise of high efficacy and relative safety. Physicians today recognize that the promise has been fulfilled . . . as evidenced by the high rate of refilled ARISTOCORT prescriptions.

Aristocort® Triamcinolone LEDERLE

Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, N.Y.

for infant formulas that are pleasant-tasting but not sweet

specify **Dextri-Maltose®**

Brand

Carbohydrate formula modifier

Controlled studies show that formulas made with cane sugar are 5 times sweeter than Dextri-Maltose formulas; corn syrup formulas are almost twice as sweet.[1]

A Dextri-Maltose formula does not "condition the child to a sweet food" when solids are introduced later on.[2] Dextri-Maltose was created exclusively for infant formulas.

Add 1 tablespoon of Dextri-Maltose to every 5 oz. of formula.

1. Research Laboratories, Mead Johnson & Company, unpublished data, available on request. 2. Holt, L. E., Jr., and McIntosh, R.: Holt Pediatrics, ed. 12, New York, Appleton-Century Crofts, Inc., 1953, p. 224.

Mead Johnson

Symbol of service in medicine

Proven

in over five years of clinical use and
more than 750 published clinical studies

Effective

for relief of anxiety and tension

Outstandingly Safe

- simple dosage schedule produces rapid, reliable tranquilization without unpredictable excitation
- no cumulative effects, thus no need for difficult dosage readjustments
- does not produce ataxia, change in appetite or libido
- does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
- does not impair mental efficiency or normal behavior

Miltown®

meprobamate (Wallace)

Usual dosage: **One or two 400 mg. tablets t.i.d.**
Supplied: **400 mg. scored tablets, 200 mg. sugar-coated tablets; or as MEPROTABS®– 400 mg. *unmarked*, coated tablets.**

WALLACE LABORATORIES/ *Cranbury, N. J.*

®TRADE-MARK

"...extraordinarily effective diuretic..."[1]

Efficacy and expanding clinical use are making Naturetin the diuretic of choice in edema and hypertension. It maintains a favorable urinary sodium-potassium excretion ratio, retains a balanced electrolyte pattern, and causes a relatively small increase in the urinary pH.[2] More potent than other diuretics, Naturetin usually provides 18-hour diuretic action with just a single 5 mg. tablet per day — economical, once-a-day dosage for the patient. Naturetin c K — for added protection in those special conditions predisposing to hypokalemia and for patients on long-term therapy.

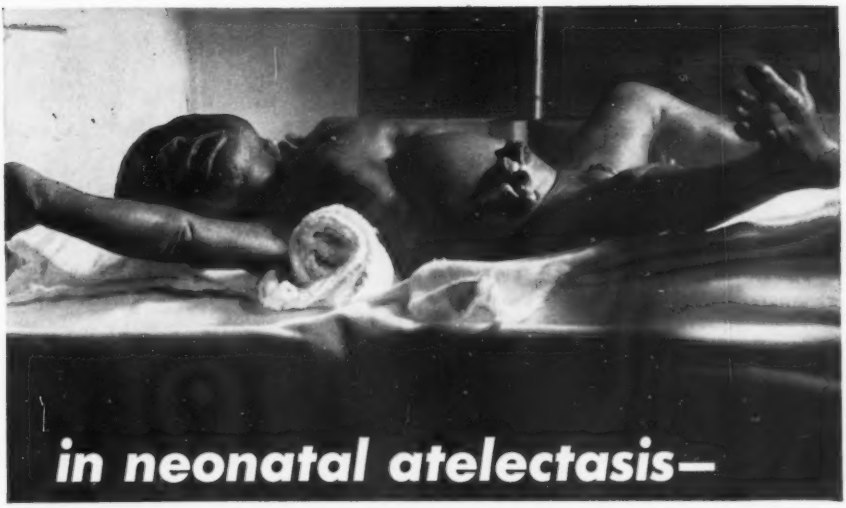
Supplied: Naturetin Tablets, 5 mg., scored, and 2.5 mg. Naturetin c K (5 c 500) Tablets, capsule-shaped, containing 5 mg. benzydroflumethiazide and 500 mg. potassium chloride. Naturetin c K (2.5 c 500) Tablets, capsule-shaped, containing 2.5 mg. benzydroflumethiazide and 500 mg. potassium chloride. For complete information consult package circular or write Professional Service Dept., Squibb, 745 Fifth Avenue, New York 22, N. Y. References: 1. David, N. A.; Porter, G. A., and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 2. Ford, R. V.: Current Therap. Res. 2:92 (Mar.) 1960.

Naturetin Squibb Benzydroflumethiazide

Naturetin c K Squibb Benzydroflumethiazide with Potassium Chloride

SQUIBB

"NATURETIN" IS A SQUIBB TRADEMARK.



in neonatal atelectasis—

ALEVAIRE®

(NONTOXIC MUCOLYTIC DETERGENT AEROSOL)

. . . results are impressive. This dreaded condition usually improved in a few hours, and it was really striking to see a cyanotic baby with gasping respirations and suprasternal retraction become relaxed and pink in such a short period of time."[1]

In the elderly patient with chronic bronchitis ". . . favorable therapeutic response is obtainable with the use of Alevaire."[2]

ALEVAIRE
is very helpful in:

- neonatal asphyxia (due to inhalation of amniotic fluid, mucous obstruction, atelectasis)
- croup • laryngitis • tracheobronchitis
- pertussis • pneumonia • bronchial asthma
- emphysema • bronchiectasis • lung abscess
- pneumoconiosis • smoke, kerosene poisoning
- poliomyelitis (respiratory complications)
- routine oxygen therapy • tracheotomy
- prevention of postoperative pulmonary complications

Alevaire is supplied in bottles of 60 cc. for intermittent therapy and bottles of 500 cc. for continuous inhalation therapy. Alevaire should not be diluted. Alevaire solution is ready for use in a concentration optimal for fine droplet stability and therapeutic efficiency.

Write for illustrated brochure.

1. Smessaert, Andre, Collins, V. J., and Kracum, V. D.: New York J. Med. 55:1587, June 1, 1955.
2. Banyai, A. L.: Geriatrics 14:621, Oct., 1959.

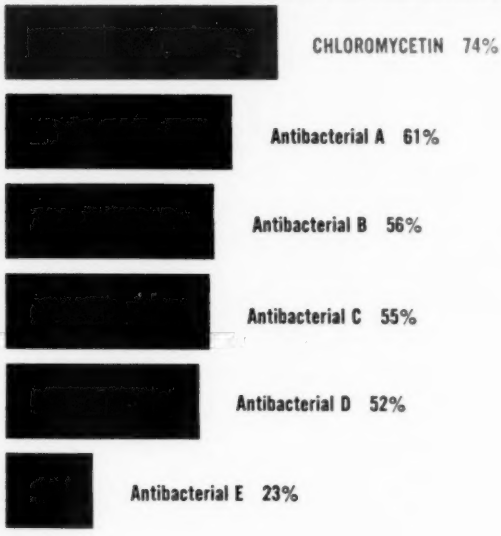
Winthrop LABORATORIES
New York 18, N. Y.

Alevaire, trademark reg. U.S. Pat. Off.

4,860 CULTURES... 74% SENSITIVE TO CHLOROMYCETIN®

(chloramphenicol, Parke-Davis)

IN VITRO SENSITIVITY OF 4,860 GRAM-POSITIVE AND GRAM-NEGATIVE PATHOGENS TO CHLOROMYCETIN AND TO FIVE OTHER ANTIBACTERIALS*



*Adapted from Goodier, T. E. W., & Parry, W. R.: *Lancet* 1:356, 1959.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

PARKE, DAVIS & COMPANY · Detroit 32, Michigan

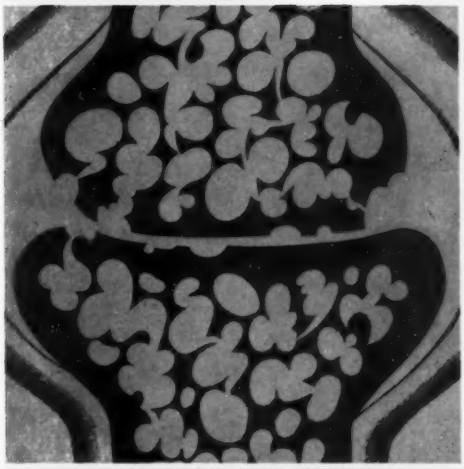
PARKE-DAVIS

in rheumatic disorders

whenever aspirin proves inadequate

Sterazolidin®

brand of prednisone-phenylbutazone



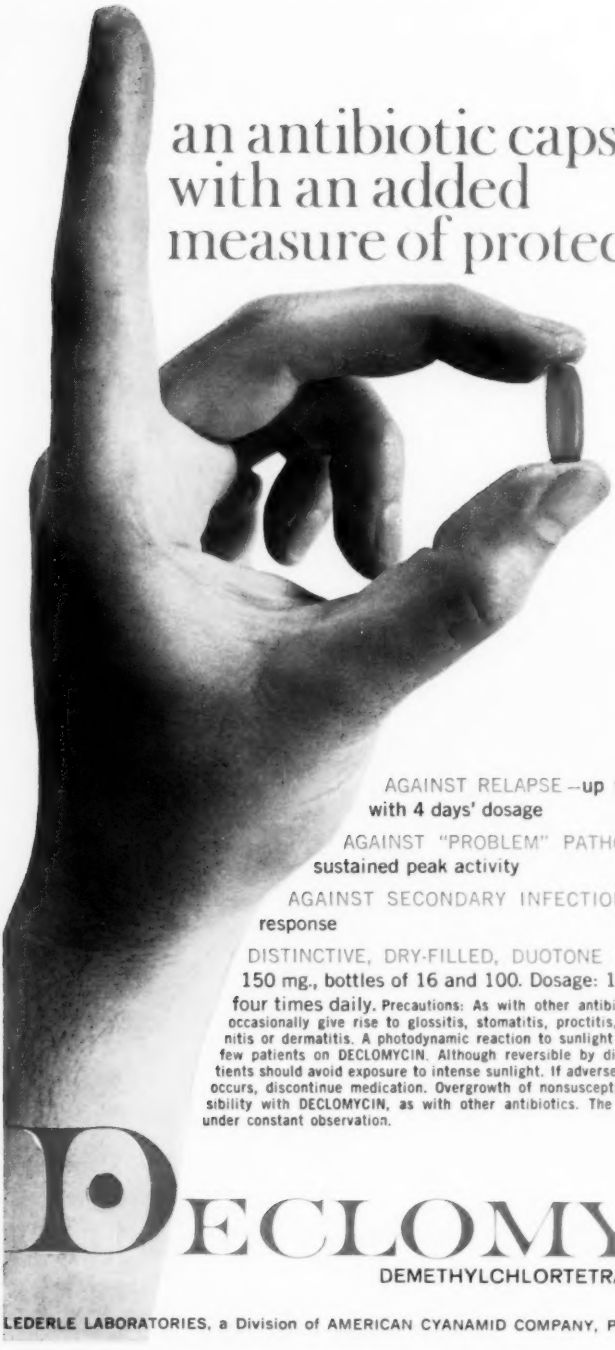
Even in the more transient rheumatic disorders, an anti-inflammatory effect more potent than that provided by aspirin is often desirable to hasten recovery and get the patient back to work.
By combining the anti-inflammatory action of prednisone and phenylbutazone, Sterazolidin brings about exceptionally rapid resolution of inflammation with relief of symptoms and restoration of function.
Since Sterazolidin is effective in low dosage, the possibility of significant hypercortisonism, even in long-term therapy, is substantially reduced.

Availability: Each Sterazolidin® capsule contains prednisone 1.25 mg.; Butazolidin®, brand of phenylbutazone, 50 mg.; dried aluminum hydroxide gel 100 mg.; magnesium trisilicate 150 mg.; and homatropine methylbromide 1.25 mg. Bottles of 100 capsules.

Geigy, Ardsley, New York

Geigy

165-60



an antibiotic capsule with an added measure of protection

AGAINST RELAPSE—**up to 6 days' activity with 4 days' dosage**

AGAINST "PROBLEM" PATHOGENS—**uniformly sustained peak activity**

AGAINST SECONDARY INFECTION—**full antibiotic response**

DISTINCTIVE, DRY-FILLED, DUOTONE RED CAPSULES—150 mg., bottles of 16 and 100. Dosage: 1 capsule (150 mg.) four times daily. **Precautions:** As with other antibiotics, DECLOMYCIN may occasionally give rise to glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis or dermatitis. A photodynamic reaction to sunlight has been observed in a few patients on DECLOMYCIN. Although reversible by discontinuing therapy, patients should avoid exposure to intense sunlight. If adverse reaction or idiosyncrasy occurs, discontinue medication. Overgrowth of nonsusceptible organisms is a possibility with DECLOMYCIN, as with other antibiotics. The patient should be kept under constant observation.

DECLOMYCIN®

DEMETHYLCHLORTETRACYCLINE LEDERLE

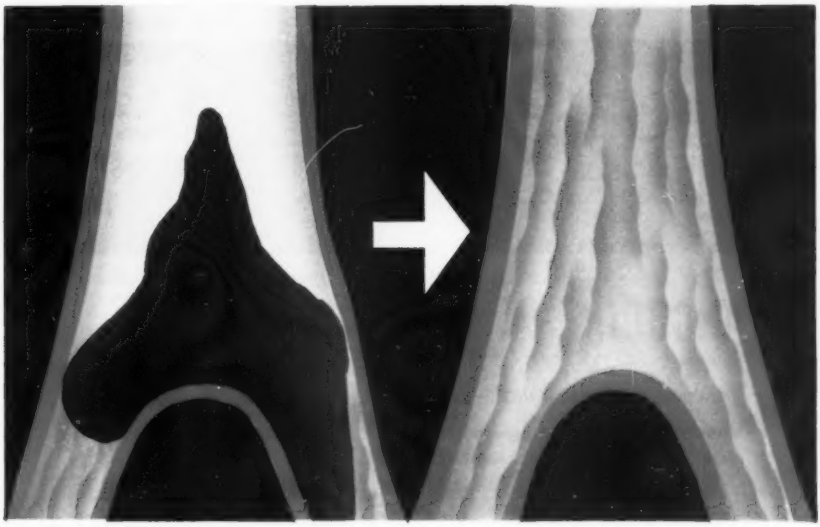
LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y.

clinical endorsement grows
as proof accumulates

ACTASE
TRADEMARK

Fibrinolysin (Human)

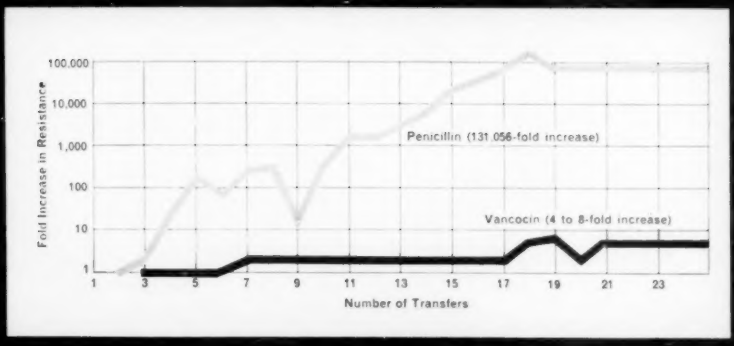
NOT JUST A NEW DRUG... *A NEW THERAPY*



Ortho

SPECIFIC FOR THE DISSOLUTION
OF INTRAVASCULAR CLOTS

an important solution in the management of resistant staphylococcus infections



DEVELOPMENT OF RESISTANCE BY STAPH. AUREUS TO VANCOCIN AND PENICILLIN—Development of resistance to Vancocin has not yet been demonstrated clinically. It is even difficult to "force" development of resistance in laboratory studies.

Lilly

QUALITY / RESEARCH / INTEGRITY

VANCOCIN®

(vancomycin, Lilly)

- Vancocin is bactericidal in readily achieved serum concentrations.
- Vancocin is effective against antibiotic-resistant gram-positive pathogens. Cross-resistance does not occur.
- Vancocin averts the development of antibiotic-resistant organisms.

Supplied:

Only as Vancocin, I.V., 500 mg., in 10-cc. rubber-stoppered ampoules. Before administration, the physician should consult essential information contained in the package.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

030102

SECOND SERIES NOVEMBER 1960 VOL. 36, NO. 11

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

CONTENTS

Contributions of Molecular Biology to Medicine . . . 725
Francis O. Schmitt

Recent Observations on the Lewis System 750
Philip Levine

Challenges in a Changing World 756
H. D. Kruse

The Early Directors of the Medical Services of the American Revolutionary Army 765
Laurence Farmer

New York Pathological Society: Abstracts 777

New York Heart Association: Abstracts—Part I . . . 782

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

Annual subscription United States and Canada $8.00. All other countries $9.00. Single copies 90c.
ADVERTISING OFFICE • 30 ROCKEFELLER PLAZA, N. Y. C. 20 • CIrcle 7-7706
Copyright, 1960 by The New York Academy of Medicine

OFFICERS AND STAFF OF THE ACADEMY – 1960

ROBERT L. LEVY, *President*

Vice-Presidents

ALBERT H. ALDRIDGE — G. JARVIS COFFIN — FRANK GLENN

SHEPARD KRECH, *Treasurer*

FREDERICK H. WILKE, *Recording Secretary*

Trustees

STUART L. CRAIG	*ROBERT L. LEVY	JEROME P. WEBSTER
HAROLD BROWN KEYES	ASA L. LINCOLN	ORRIN S. WIGHTMAN
*SHEPARD KRECH	JOHN L. MADDEN	*FREDERICK H. WILKE
SAMUEL W. LAMBERT, JR.	WILLIAM BARCLAY PARSONS	ROBERT H. WYLIE
	BENJAMIN P. WATSON	

Council

The President — The Vice-Presidents — The Trustees

The Treasurer — The Recording Secretary

The Chairmen of Standing Committees:

ANTHONY C. CIPOLLARO, *Admission*	WILLIAM C. WHITE, *Library*
MILTON J. GOODFRIEND, *Public Health*	JOHN L. MADDEN, *Medical Education*
ARTHUR M. MASTER, *Special Studies*	G. JARVIS COFFIN, *Sections*

HOWARD REID CRAIG, *Director*

GERTRUDE L. ANNAN, *Librarian*

HARRY D. KRUSE, EXECUTIVE SECRETARY, *Committee on Public Health*

AIMS C. MCGUINNESS, EXECUTIVE SECRETARY, *Committee on Medical Education*

IAGO GALDSTON, EXECUTIVE SECRETARY, *Committee on Special Studies*

ROBERT L. CRAIG, EXECUTIVE SECRETARY,
Committee on Publications and Medical Information

THOMAS L. STAPLETON, EXECUTIVE SECRETARY,
Committee on Public Relations and Financial Development

ROBERT M. BRERETON, *Business Manager*

DAVIS POLK WARDWELL SUNDERLAND & KIENDL, *Legal Counsel*

Library Consultants

JANET DOE, CURT PROSKAUER

EDITORIAL BOARD

JEROME P. WEBSTER, *Chairman*
GERTRUDE L. ANNAN
MARGARET BEVANS
CHARLES E. KOSSMANN
CHARLES A. RAGAN, JR.
ROBERT L. CRAIG,
Secretary and Editor

* Ex Officio

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 36, NO. 11 NOVEMBER 1960

CONTRIBUTIONS OF MOLECULAR BIOLOGY TO MEDICINE*

*The Ludwig Kast Lecture***

FRANCIS O. SCHMITT

Institute Professor, Department of Biology, Massachusetts Institute of Technology
Cambridge, Massachusetts

MOLECULAR biology may be characterized as that branch of the life sciences in which the attempt is made to investigate biological processes at or near the molecular or macromolecular level. The conceptualization of the problems and the design of experiments are largely biophysical and biochemical in nature. Molecular biology represents by far the most highly developed segment of biophysical science at the present time (see, for example, the recent study program in biophysical science)[1]. The widespread impact of molecular biology on biomedical science compares with the fundamental advances that followed the discovery and exploitation of the role of ionization in biomolecules during the early history of physical chemistry near the turn of the century.

* Presented at the Third Annual Postgraduate Week, replacing the *Graduate Fortnight* of former years, of The New York Academy of Medicine, October 5, 1959.

Original investigations reported in this paper were supported by research grant E-1469 from the National Institute of Allergy and Infectious Diseases of the U.S. Public Health Service to the Massachusetts Institute of Technology.

** In honor of Dr. Ludwig Kast, who first suggested the *Graduate Fortnight*.

Basic to molecular biological research is the attempt to isolate, purify, and characterize the macromolecular species responsible for function at the various levels of complexity, *e.g.*, cells, tissues, and organisms. This requires application of the entire battery of biophysical, physicochemical, and biochemical methods. Sometimes it is necessary to refine or modify existing methods to make them more applicable to the complex biological material under study and occasionally to invent and develop entirely new techniques. The molecular biologist's task is the analytical one of disentangling the complex aggregates of protoplasm into their respective "molecular" entities, whose constituent atoms and chemical groups are held together primarily by covalent forces, or into macromolecular entities, in which a few covalent chains are linked firmly by secondary bonds to form biologically, physically, and chemically characteristic arrays. After the molecular or macromolecular entities have been isolated in relative purity, the analysis proceeds to the investigation of the chemical composition and the physicochemical properties that emerge from each complex array of constituents.

Particularly in the biomedical area the temptation arises, even before the analysis has progressed much beyond the crude beginnings of a characterization of the macromolecular entity of interest, to be diverted into an investigation of the role of the supposed entity in normal or abnormal function. This is understandable in view of the human suffering that would be alleviated by a breakthrough in an understanding of underlying molecular mechanisms. Experience has clearly demonstrated that advance will be most rapid if the situation in normal cells and tissues is investigated before, or at least concomitant with, the attempt to unravel the more intricate complexities of the pathological situation. Similarly, it is most rewarding in the long run to persevere in the physical and chemical characterization of the molecular entities before attempting to explain how alterations and interactions of these entities produce normal function. Frequently the complexity is such that direct frontal assault on the problem stalls, and new leads must be uncovered by empirical investigations or by the refinement of techniques. The examples we have chosen to illustrate molecular biological research will, I hope, heavily emphasize the importance of this ceaseless urge to isolate, analyze, identify, and characterize.

However, the isolation, identification, and characterization of the molecular or macromolecular entities in a biological process are of

limited biomedical significance unless followed by an investigation of the manner in which function is subserved by the molecular entity, and in particular how the biological system succeeds in attaining that homeostatic control of events that permits it to respond adaptively to each situation. This second type of activity is far more complex and demanding on the patience and dedication of the investigator than the first. Correspondingly, the differentiation between the more physically or chemically oriented investigators on the one hand and those more biologically or medically oriented on the other hand is more clearly evidenced at this level of activity.

Having demonstrated and defined the fundamental importance of the investigations of the biophysical and biochemical analyst in molecular biology, we shall document the equally significant contributions of the molecular *integrationist* who studies the over-all, highly regulative reactions by which the molecular entities play their role in the harmonious interplay of the protoplasmic microcosmic mechanisms.

Finally, we shall add a practical note by making a case for giving appropriate professional encouragement, support, and status to the investigators of the second type—the molecular integrationists—who, because they operate mostly between or at the periphery of traditional university-established disciplines, may fail to achieve the stable status enjoyed by their colleagues in the more sharply defined areas of biomedical science.

Some Case Histories of Molecular Biology

1. *Genetics, Molecular Coding, Viruses, and the Mechanism of Infection*

The discovery of the molecular nature of the genetic code that determines heredity and of the manner in which this code directs the biosynthesis of protoplasmic constituents represents the most dramatic chapter in present-day molecular biology. The genetic problem also serves to illustrate both the power and the limitations of the investigation of the molecular basis of a complex biological process.

Mendel's experiments in 1866 demonstrated a quantitative relationship between genetic characteristics of parents and offspring. His fundamental discovery was lost on the naturalistic, description-minded biologists of the day. However, at the turn of the century, descriptive cytological studies succeeded in demonstrating that the genetic deter-

miners are in the nucleus of the cell and, more precisely, in the chromosomes, whose contortions and maneuvers during mitosis and meiosis seemed designed to provide precisely the quantitative genetic regulation demonstrated by Mendel.

The chemical assault on the problem begins with the work of Miescher, who isolated and crudely characterized nucleic acid, and P. A. Levene[2], who brought chemical precision to the analyses and focused attention on the tetranucleotide, containing one or all four of the known types of nucleotides, as the "molecule" of nucleic acid.

To those of us who were students during those early formative days of the story of genetics, the gaps between the tetranucleotide, the chromosomes, and the complex regulative mechanisms of embryogenesis, growth, and development were wide indeed; few aspired to an integrated physical and chemical attack on the fundamental genetic problem. It is hard to say whether the revelation of the macromolecular nature of deoxyribonucleic acid (DNA) in the mid-'20s would have been recognized as a fundamental discovery or whether, like Mendel's discovery, it would have had to wait a generation or two for the flowering of its full significance.

What actually provided a powerful forward thrust to genetics was not molecular biology, but a highly perceptive utilization of rather empirical data on the effect of x-rays and high-energy radiation on unitary genetic characters. The big push in genetics was not yet ready to be focused on the molecular basis of the process. Although the analytical biologists were beginning to "zero-in" on the nature of the gene, nucleic acid and nucleoproteins were too complex to appeal to many of the pure chemists and biochemists of the day. In fact, physicochemical discoveries indicated that the true molecule is not a tetranucleotide of about 1,200 molecular weight. When the chromosomal material was extracted with milder methods, the nucleic-acid molecule was shown to be gigantic in size, having molecular weight in the millions. This was one of the early contributions of macromolecular biophysical chemistry.

Even then, with fairly good evidence that the substance of the nucleus that is concerned with genetic coding must be a giant linear macromolecule, it was not obvious how such molecules could serve as the physical basis of genetic phenomena; few biophysical or biochemical recruits were attracted into the field. The fundamental nature of the

problem still lacked focus. Not quite enough of the macromolecular structure was understood to reveal the fundamental clue.

The study of the crystallography of biologically important macromolecules, especially the proteins, begun by Herzog[3], Meyer and Mark[4], and most effectively pioneered by Astbury[5] during the '30s, had to be set aside for "more important matters" during the early forties. Then with improved techniques of x-ray-diffraction analysis and with better methods of preparation of highly orientated nucleic-acid macromolecules, diffraction data were obtained[6, 7] which led Crick and Watson[8] to propose the two-strand structure of DNA now commonly accepted. Here at last was a model that could tie together a vast body of genetic evidence, particularly that from the rapidly expanding use of viruses and microorganisms for genetic studies, into a self-consistent fabric of molecular biology. Ingenious use of isotopic tracers[9] further supported the fundamental hypothesis that one of the two strands of DNA derives from the paternal and the other from the maternal organism.

Improvements in electron-microscopic techniques then permitted direct visualization of the DNA macromolecules, lending support to the conclusions about the size and shape of DNA, deduced from physicochemical evidence.

The discovery of the two-strand helix, though a natural development in the growing understanding of intramolecular organization, particularly helical structure, caused the field of molecular genetics to "go critical", to borrow a phrase from atomic-reactor technology. Data began fitting into place. With mounting success more able investigators moved into the field, particularly from physics and microbiology, and a chain reaction started which brought genetics into the limelight of interest in the life sciences (see the excellent review by Perutz)[10].

Precisely how an array of purine and pyrimidine nucleotides along a giant DNA polymer codes all the complex biosynthetic and developmental processes still remains far from clear, but the second stage, in which the details of the molecular physiology and biochemistry of the coding process are being investigated, is now in full swing. DNA is pictured as coding RNA, which in turn codes protein, specifically the enzymes required to fashion all the critical biomolecules from pauciatomic precursors in the metabolic pool. This concept is no doubt an oversimplification, but it has provided a vision that has moved many to join in the highly detailed biochemical investigation of the bits and

pieces that might fit into the currently prevailing pattern for the genetic jigsaw puzzle.

The ultimate biological problem of the nature of the positive and negative feed-back control mechanisms by which the multitudinous reactions are channeled along lines required to produce the mature organism involves complex *patterns* of interactions. The discovery of the nature of the primary, but not the only, directive code (DNA) is a necessary, though not sufficient, clue. Many biologists believe that a larger *pattern* of determination which is highly dynamic and partakes of "field" properties is in operation. To what extent such organizing processes may involve physical and chemical processes not presently definable will not be known until more information is gained about the parameters which determine the interacting and evolving morphodynamic fields.

The case history of genetic coding includes further chapters of great medical significance. These deal with the molecular mechanism of virus replication and the light this throws on the nature of infection. One reason why this area of molecular biology progressed rapidly after application of electron-microscopic techniques is that all the actors in the drama—the invading viruses and the microorganisms—are small enough to be seen in their entirety in the field of the electron microscope, which, at high resolution, can reveal details down to molecular size (*ca.* 10 Å).

It now appears that in the bacterial virus (bacteriophage) the DNA genetic determiners are compactly coiled in the "head"; when the virus fixes itself onto the bacterium, the DNA is injected through its hollow "tail" into the protoplasm of the bacterium. There the invading DNA code proceeds to commandeer the chemical economy of the invaded cell by directing the biosynthetic processes of the latter to produce many replicas not only of the invading code, the DNA strand, or "chromosome," but also the accessory parts of the virus "body": the head membrane, tail protein, tail strands, and screw thread. The invaded cell is converted into an assembly plant in which, after fabrication in its protoplasm, the various parts are assembled into complete viruses (Figure 1 B, taken from the excellent paper of Horsfall)[11]. The invaded cell, now packed with viruses, ruptures its membrane and disintegrates. This process dramatically illustrates the fundamental nature of infection and exposes the various aspects, particularly the biosynthesis of the

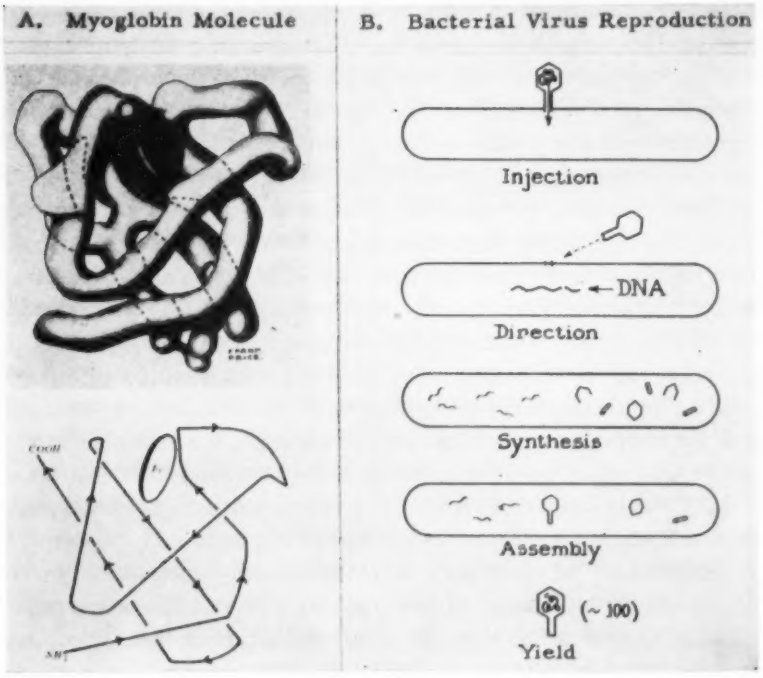


Fig. 1

A. Intramolecular structure of myoglobin molecule according to Kendrew *et al.*[14] Above, drawing of the polypeptide chain deduced from Fourier synthesis with resolution of 6 A. Below, same deduced from 2 A resolution Fourier synthesis.

B. Diagrammatic representation of events in bacterial virus reproduction in a bacterial cell. (After Horsfall)[11].

components of the infecting agent, to the scrutiny of the biochemist, who may hopefully be able to discover means by which essential steps in the synthetic reaction chain may be blocked by chemical agents which will not interfere with the normal metabolic processes of the host cell.

At a more fundamental level of molecular biology, the experiments of Avery, Macleod, and McCarty[12] had demonstrated that DNA could be isolated from one strain of bacteria and, after careful purification, combined with a different strain, whose native DNA had also been removed, with the result that the heredity of the reconstituted receptor bacterium is thereby determined by the DNA of the donor-cell type. This demonstration of the "transforming", heredity-determining poten-

tialities of DNA opened up a vast new field of biomedical research of far more profound significance than was realized at the time: genetic determination and infection itself can be produced by a purified chemical substance, DNA*. This poses the significant possibility that certain degenerative diseases, such as cancer, may result from the effects of a DNA code made malignant possibly by endogenous reactions** in the host cells as well as by virus-like invaders such as are known to cause certain types of cancer in rabbits and chickens[13]. We know now that large macromolecules gain entrance into cells by an infolding of the surface membrane. Foreign and possibly malignant DNA that might be so admitted would presumably encounter, as a first powerful line of the cell's defense, DNA-depolymerizing enzymes which would disrupt the invading code and add the resulting nucleotides to its own metabolic pool. However, if such defenses are not adequate, it is possible that such foreign DNA might produce serious pathological changes.

In this case history of molecular genetics, emphasis has been placed on DNA. Its close counterpart RNA is also vitally involved, presumably as an intermediate between DNA determiners and protein-catalytic effectors. When the detailed structure of RNA is revealed, new secrets will doubtless suggest other ways in which the inherited, preformed code determines not merely the synthesis of cell constituents in the adult organism, but also the steps in differentiation, axial symmetry determination, and other field-like characteristics of growth and development.

2. *Protein Structure*

The significance of an understanding of the detailed structure of proteins has long been appreciated. The development of biophysical and biochemical tools by which such knowledge may be gained has now reached a level where crucial data are rapidly accumulating. The following examples illustrate important consequences of such discoveries.

X-ray-diffraction techniques, painstakingly developed, particularly by Kendrew and Perutz in Cambridge, have revealed the contour of the single polypeptide-chain which, when folded in a specific manner and associated with the physiologically active heme group, constitutes myoglobin. This was accomplished by Kendrew with a resolution of

* Although such DNA may be very pure, the possibility that very small amounts of protein or other "impurity" are still present, possibly as an intrinsic constituent, cannot be excluded.

** Such reactions may, of course, be responsive to genetic factors in the host which are evoked after a certain stage has been reached in the life history of the cell or organism.

6 Å. Having pushed the resolution to 2 Å, Kendrew and associates[14] have recently detected the α-helix in the polypeptide chain (Figure 1 A). When it is remembered that the myoglobin molecule consists of 153 amino-acid residues with a molecular weight of 17,000, the magnitude of these contributions is better grasped. Perutz and associates[15] have succeeded in "seeing" the four globular particles of hemoglobin constituting an aggregate of two half-molecules, four polypeptide chains, and four heme residues, totaling 67,000 in molecular weight. With such detailed information it may become possible to discover the way in which the protein moiety determines the combining characteristics of the heme for oxygen, a process of vital importance in the biochemistry and physiology of respiration and in the catalytic and electron-transporting properties of the heme-containing enzymes and carriers (cytochromes).

At a somewhat grosser level, Hall's[16] method of depositing macromolecules on a freshly cleaved mica surface before shadowing with heavy metal atoms has permitted direct electron-microscopic visualization of macromolecules of molecular weights down to about 50,000 (Figure 2). This has been of enormous value not merely as an independent check on the conclusions of the indirect methods of physical chemistry[17], but in revealing structural details not readily deducible by indirect means; this is well illustrated in the case of fibrin, discussed below.

Analytical biochemistry has also been a major contributor to molecular biology. The method of determining amino-acid sequence in native polypeptide-chains, pioneered by Sanger[18] in the case of insulin, is now being routinely employed in the analysis of proteins and peptides generally.

The case of sickle-cell anemia illustrates admirably the significance of the finest details of molecular structure, not only for the organism, but for whole populations. In sickle-cell anemia the red cells, when in the venous circulation, assume irregular, elongated shape (like little sickles), impeding circulation and leading to an acute hemolytic anemia. Birefringence changes suggest that underlying these phenomena is the tendency of the hemoglobin molecules to aggregate in elongate columns to form paracrystalline arrays which change the shape of the erythrocytes into elongated sickles.

Applying his chromatographic "fingerprint" method, Ingram[19] dem-

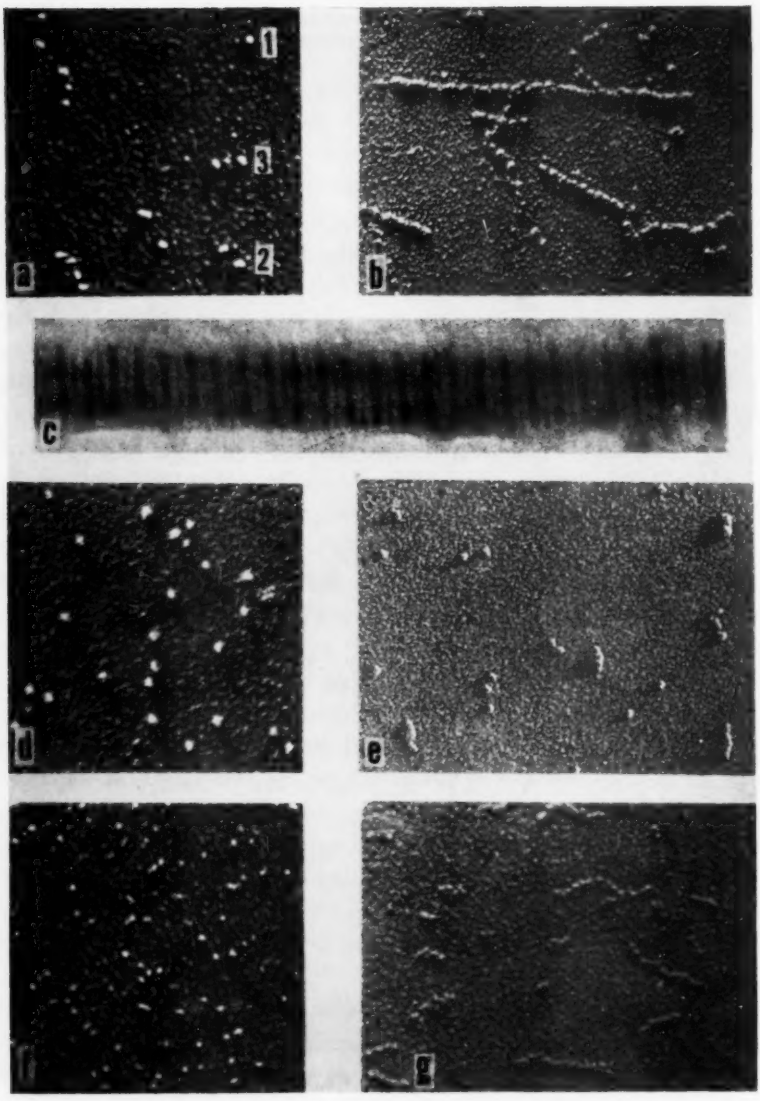


Fig. 2—Electron micrographs of protein molecules (courtesy of Dr. C. E. Hall, Massachusetts Institute of Technology).

a. Bovine fibrinogen. Intact molecules are triads (3). Fragments produced by disruptive forces during drying form monads (1) or diads (2). Magnification 156,000.

b. Intermediate polymers: linear aggregation of fibrinogen molecules produced by action of thrombin. Magnification 100,000.

c. Fibrin fibril stained with phosphotungstic acid. Axial period $\cong$ 230 A. Magnification 200,000.

d. Alkaline phosphatase, from *E. coli*. Magnification 150,000.

e. Normal rabbit gamma globulin. Magnification 100,000.

f. Pepsin. Magnification 150,000.

g. Polyglutamic acid. Magnification 135,000.

onstrated that sickle-cell hemoglobin differs from normal hemoglobin by a change in but one amino-acid (of the 300 amino-acid residues in the half-molecule); valine is substituted for glutamic acid. Ingram also suggested how a single gene alteration might cause this subtle change in the hemoglobin molecule, leading in turn to serious consequences for the organism and to vast sociological changes in African populations (the genetic defect is found almost exclusively in the Negro).

This is a prime example of what Pauling[20, 21] calls "molecular disease", *i.e.*, a disease produced by an alteration in a particular molecular species. Ingram's elegant experimental work has demonstrated the nature of that change. However valuable as a milestone in molecular biology, this information in itself is of little clinical aid to sufferers of the disease. But, hopefully, subsequent investigation will soon reveal the biochemical mechanisms by which the defect in hemoglobin biosynthesis occurs. This may lead to a method by which the abnormal synthetic processes may be blocked or caused to produce a less noxious result.

3. *Protein Fibrogenesis and its Homeostatic Control*

The following two case histories are presented because they illustrate problems of vast medical significance in which are well represented both aspects I wish to emphasize: the importance (a) of identification and characterization of the molecule involved and (b) of determination of the complex homeostatic processes that regulate the generation and ordering of these molecules adaptively to the needs of the organism. These are blood clotting and collagen fibrogenesis.

A. *Blood Clotting.* The basic reaction in blood clotting is the conversion of soluble fibrinogen macromolecules into insoluble fibrin clot fibers. It has been known for more than a century that this process is mediated by an enzyme, thrombin, the formation of which, from its precursor prothrombin, is under the control of a highly complex system of enzymes and anti-enzymes, kinases and anti-kinases, factors, co-factors, specific ions, inhibitors, et cetera. Because the clotting process can be readily studied in a rough way without detailed knowledge of the structure and composition of the structural unit (the fibrinogen macromolecule), investigation of the regulatory mechanisms received far heavier emphasis in the early development of the field than did the frontal attack on the problem of the fibrinogen molecule. Perhaps this helps explain the rather controversial and confused state of clotting

theory, though the over-all process is doubtless sufficiently complex to require many years of patient research, whichever aspect was stressed first. A clear exposition of the essential features of the homeostatic mechanisms of blood clotting is given by Waugh[22].

Physicochemical investigations have revealed the size and shape of the elongate fibrinogen macromolecules and have suggested the manner in which, after enzymatic activation, they may aggregate to form intermediate polymers; after a critical size is reached, these spontaneously aggregate end-to-end to form the polymeric fibrin. End-to-end and lateral aggregations apparently are facilitated by enzymatic splitting-out of two peptides from particular regions of the native monomer.

Early large-angle x-ray-diffraction studies[23] showed that fibrinogen and fibrin are members of the so-called K-M-E-F class, or, as we now say, the polypeptide chain is wound in an α-helix configuration. However, little x-ray work with modern methods has been done on this protein, and, so far as the author recalls, no small-angle studies have been published. This is regrettable in view of the fact that, when prepared under appropriate conditions, fibrin fibrils manifest an axial repeat period of about 240 Å as seen in the electron microscope[24] and there is intraperiod banded fine structure[25].

Recently Hall[26] has applied his technique for visualizing macromolecules with the electron microscope to the study of fibrinogen and the mechanism of the clotting process. Certain of his results, shown in Figure 2, a-c, could hardly have been discovered by the use of any other biophysical method. His electron micrographs portray fibrinogen not as a simple rodlet, but as three spheres connected by a thin strand near the limit of resolution. The axially periodic band structure presumably results from an aggregation of such molecules after an apparent contraction of the axial connecting thread. If this contraction is not an artifact, these results suggest that two constituents are present in the "molecule". The individual three-lobed fibrinogen molecules and polymeric aggregates thereof (fibrin) are shown in Figure 2.

It seems apparent that if the details of intramolecular structure and amino-acid composition of fibrinogen and fibrin* were known, much of the controversy and confusion among investigators of the clotting

* For purposes of simplification the discussion has been limited to fibrinogen and fibrin with little reference to other essential components such as prothrombin, thrombin, et cetera. However, the main line of the argument probably applies also to them, namely that progress would be faster if more emphasis were placed on determining their fundamental biophysical and biochemical properties.

mechanism might have been avoided and real progress accelerated.

Blood clotting serves as a prototype of complex regulative homeostatic mechanisms by which vital processes of structuration can be adapted to the immediate and long-range needs of the organism. Whether other types of fibrogenesis will be found to follow this pattern remains to be seen.

B. *Collagen Fibrogenesis.* Progress in the investigation, at the molecular level, of connective tissue, especially collagen fibers, has probably been more extensive in the last quarter century, and particularly in the last decade, than in all previous time combined. The key to this advance has been the isolation and identification of the unit of collagen structure, the soluble "tropocollagen"* macromolecule, and the determination of the intramolecular architecture of the constituent polypeptide chains.

When the insoluble, seemingly inert collagen fiber was the only material with which to work, the investigation of collagen attracted meager interest among biophysicists and physical chemists. The characteristic large-angle x-ray pattern of the collagen class had been identified, and efforts had been made to deduce the configuration of the constituent polypeptide chains[27, 28], but the relationship between such data and the collagen *molecule* was unexplored. Little was known at the molecular level as to how collagen, presumably synthesized in fibroblasts, becomes incorporated into stout fibers of high tensile strength. Less was known about the complex regulatory processes by which, for example, in wound repair, collagen fibrils are laid down in the precise amount and pattern appropriate to the site at which the wound occurred.

The collagen case is the reverse of that of blood clotting; in the latter the regulatory processes were widely investigated before much detailed knowledge was obtained about the structure and properties of the fibrinogen and fibrin molecules. As a result of the recent substantial advances in its biophysical and biochemical analysis, collagen has become probably the best known of fibrous proteins.

When treated with phosphotungstic acid (PTA) as an "electron stain", collagen fibrils present a banded appearance in the electron microscope. The axial repeat is of the order of 700 Å, and some 10 to

* The soluble collagen macromolecules were termed "tropocollagen" because they are capable of "turning into" or forming the native collagen structure with its characteristic 640 Å axial repeat[29]. The term also helps to distinguish this macromolecule from other collagen fractions and avoids uncertain or erroneous conclusions concerning precursors implied in names such as procollagen or precollagen.

12 intraperiod bands may be observed in high-resolution electron micrographs, each band having characteristic position and intensity (Figure 3). It was early assumed that such structures result from a parallel packing of protofibrils[29], *i.e.*, collagen linear polymers, the bands indicating side-chain loci which combine preferentially with the PTA and which form regions of relative disorder as compared with the poorly staining interband, ordered regions[28]. By a combination of electron-microscopic and chemical-analytical studies it has been shown[30, 31] that it is the basic, specifically the arginine, side-chains that are thus stained with PTA. The axial repeat observed in the electron microscope corresponds well with the period deduced from small-angle x-ray diffraction (640 Å in dried preparations, 700 Å in undried preparations). Therefore it was generally supposed that the collagen molecules have this length, *ca.* 700 Å.

From improved large-angle x-ray-diffraction data, Rich and Crick[32] deduced that collagen is a three-strand molecule, the constituent polypeptide-chains describing a rather lazy helical course (Figure 3). Though this structure has not yet been definitively proven, it is consistent with all available data.

It had long been known that certain types of collagen (*e.g.*, rat-tail tendon, fish swim-bladder) are soluble in dilute acid and that collagen fibrils can be reconstituted from such acid solutions by elevation of pH and adjustment of the ionic strength. Fibrils thus reconstituted from acid-soluble collagen have the same band structure as native collagen fibrils[29].

Collagen in various types of tissues was later demonstrated to be soluble in acid citrate solutions[33]. When such solutions, after dialysis against water, were examined in the electron microscope, a new, so-called "fibrous long-spacing" (FLS) type was discovered[34]. The tentative conclusion was drawn that the repeat period observed in this new "long-spacing" modification of collagen represents the true length of the collagen macromolecule. It was subsequently demonstrated that a second isomorphic modification of collagen, with similar long-spacing but with non-fibrous character, could be produced simply by adding adenosine triphosphate or certain types of negatively charged polyelectrolytes to acid solutions of collagen[35]. This so-called "segment long-spacing" (SLS) type has a characteristic, asymmetric band-pattern when stained with PTA. At high resolution this band pattern (Figure 4) provides a

PHASES OF COLLAGEN INVESTIGATION

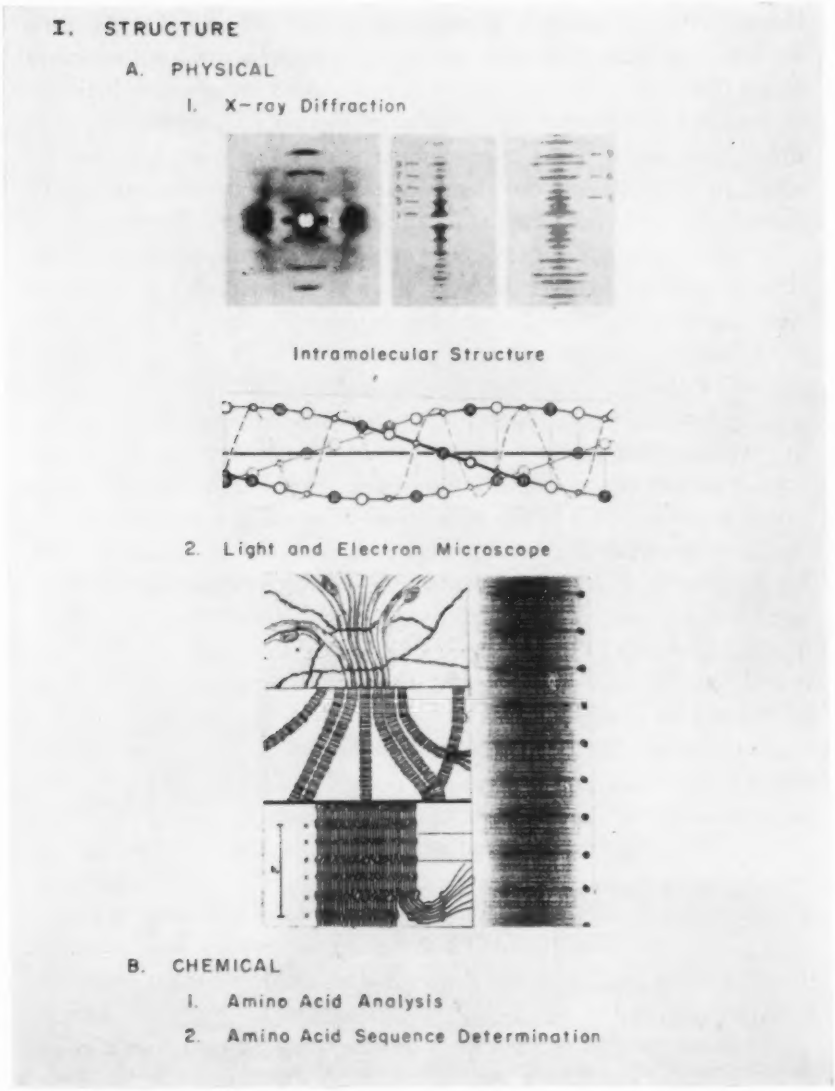


Fig. 3

First phase of collagen investigation: descriptive physical and chemical morphology. X-ray diffraction patterns are: (left) large-angle pattern of stretched rat-tail-tendon collagen from Randall[65]; (center) small-angle patterns of kangaroo-tail-tendon collagen (orders marked), moist preparation; (right) after brief exposure to water and drying under tension (from Bear, Bolduan, and Salo[66]). Diagram of helix structure (courtesy of A. Rich). Electron micrograph of calf-skin collagen fibril reconstituted from solution, stained with phosphotungstic acid. Magnification 97,000 (courtesy of A. J. Hodge).

"molecular fingerprint" of the collagen molecule or macromolecule, *i.e.*, since the thin elongate macromolecules are all oriented in the same direction and since their ends are in exact register, the band structure of SLS observed at high resolution in PTA-stained preparations indicates the location of the basic, particularly the arginine, side-chains. Recently it has been found[36] that after staining with cationic uranyl salts, by which presumably only the glutamic-acid and aspartic-acid residues are stained, the bands occur at the identical levels as those observed in PTA preparations, though the intensities of the bands under the two conditions of staining are quite different (Figure 4). This result is consistent with the view that lateral interaction is primarily through electrostatic bonds between acidic and basic side-chains, and with the "quarter-stagger" hypothesis, *i.e.*, that adjacent protofibrils are out of register with each other by one-quarter of a macromolecular length, giving rise to the characteristic 700 Å repeat pattern of native collagen[37]. It was postulated that the soluble macromolecule, called tropocollagen, has a length four times that of the axial repeat observed in native fibrils.

The hypothesis of a soluble tropocollagen molecule was confirmed by Boedtker and Doty[38] from physicochemical measurements on collagen solutions prepared by a method which removes the longer polymeric protofibrils. Macromolecules of tropocollagen having the predicted lengths were subsequently observed directly in the electron microscope by Hall[17, 39].

In investigations of sonically irradiated solutions of collagen, Hodge and Schmitt[40] observed dimeric and polymeric forms which led them to hypothesize the existence of peptide end-chains extending one from either end of the tropocollagen macromolecule. One of these chains (the A chain) is *ca.* 100 Å long and is thought to contain acidic and possibly tyrosine residues, while the other (the B) end-chain is somewhat longer, 180–200 Å, and is thought to contain some basic residues. Polymerization of tropocollagen presumably occurs by intertwining of A and B end-chains in a two-chain helix (Figure 4).

The above hypothesis was supported by results obtained in a study of the effect of proteolytic enzymes on soluble collagen[41]. It had long been supposed that proteolytic enzymes (other than collagenases) have little or no effect on collagen. However, it was found that trypsin and certain other proteases reduce the viscosity of collagen solutions, presumably by depolymerization of the polymeric protofibrillar strands.

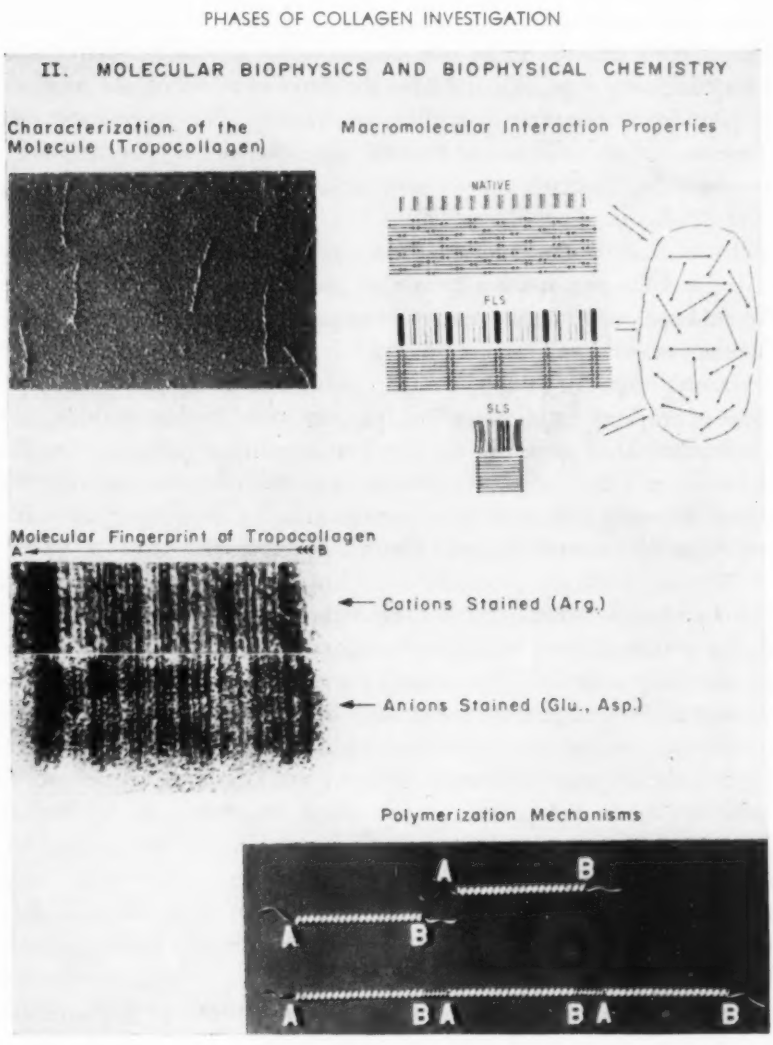


Fig. 4—Second (current) phase of collagen investigation: molecular biophysics and biophysical chemistry; characterization of the soluble macromolecule and its linear and lateral aggregation properties.

Moreover, trypsin-treated tropocollagen is no longer able to polymerize on dialysis against water or to reconstitute native-type fibrils on dialysis against salt in the cold, suggesting that the proteolytic enzyme affects one or both end-chains, so that normal polymerization is impossible. This conclusion was supported by the demonstration of the presence of peptides in the enzyme-treated preparation. The supposition that tyrosine may occur in one or both of the end-chains was borne out by observing high specific radioactivity in an acid fraction after labeling with I^{131}.

In the skin of most animals, particularly in growing animals, tropocollagen monomers and polymers exist in a form readily extractable in the cold with neutral salt solution of about 0.2—0.5 N; when such solutions are heated to 37°, a gel of native-type fibrils is formed[42]. Gross[43] has found that salt-soluble collagen disappears from the connective tissue in scorbutic guinea pigs and reappears shortly after ascorbic acid is administered. Apparently the extractable collagen, produced by the fibrocytes and dissolved in the ground substance of connective tissue in normal growing animals, is incorporated into the fixed fibrils by polymerization and quarter-staggered lateral aggregation.

The tropocollagen macromolecule has been characterized only in roughest outline. Much remains to be determined, particularly concerning the structure, composition, and properties of the end-regions, which are especially critical in the process of polymerization and fibrogenesis. Changes in these crucial areas that may seem trivial in nature, for they involve but few of the more than 3,000 amino-acid residues of the whole molecule, may profoundly influence the properties of the macromolecule. When only a few peptide-bonds are broken in the critical end-regions by proteolytic enzymes, the tropocollagen macromolecules may lose their ability to polymerize and form fibers[41].

Sufficient information is probably now known about the tropocollagen monomer to justify making a cautious beginning in the investigation of the complex homeostatic-mechanisms that regulate the laying down of fibrous collagen in growth and development and in the repair of wounds or experimentally produced defects. Investigations have already been undertaken on certain pathological states. One of the most dramatic of these is lathyrism, a condition which can be produced experimentally by injection of any of a series of homologous compounds, the one usually employed being β-aminopropionitrile. According to

Levene and Gross[44], the collagen from animals so treated is essentially normal in all respects except that the tensile strength of the collagenous fibers is very low; in extreme cases the integrity of the connective tissue is not maintained. The results suggest that some substance, possibly a protease, produced in the organism as a result of ingestion of the lathyritic agent or injection of the reagent in experimental cases, may affect end-chains in a manner such as to prevent end-to-end polymerization and to depolymerize collagen fibers already formed[41].

As in the case of blood clotting, the formation, from soluble precursors, of collagen fibers and their deposition in the connective tissue in appropriate amount and pattern of organization and at the proper time, is essential for life; derangement of the pattern of collagen fibrogenesis may lead to serious pathological conditions, some of which are usually grouped under the heading of aging processes. One might expect that, as in the case of blood clotting, the reactions involved in the various steps of collagen fibrogenesis may be under rigid homeostatic control by means of complex positive and negative feedback mechanisms implicating enzymes, pro-enzymes and anti-enzymes, factors and co-factors, kinases and anti-kinases, specific ion effects and probably also hormones.

Given a working knowledge of the main features of the soluble tropocollagen macromolecule and its interacting end-chains as a standard point of control reference, the investigator is in a position effectively to search for the regulatory mechanisms, to discover both the chemical composition and structure of the precursor tropocollagen as produced by the fibroblasts and also the subtle chemical alterations that change this soluble precursor macromolecule to one capable of polymerizing and aggregating in characteristic manner to form stable fibers of high tensile strength.

In Figures 3 to 5 is depicted the type of information obtained in three phases of collagen investigation. The first of these (Figure 3) was concerned primarily with structure, both physical and chemical. Valuable as they were in revealing the nature of the collagen helix and the organization of the native fibrils as seen with high-resolution electron microscopy, such structural studies gave no direct information about the status of the molecule itself. We now understand why this is the case and indeed why the structural evidence was actually misleading in this respect (*e.g.*, suggesting that the molecule is 640 Å long). Many bio-

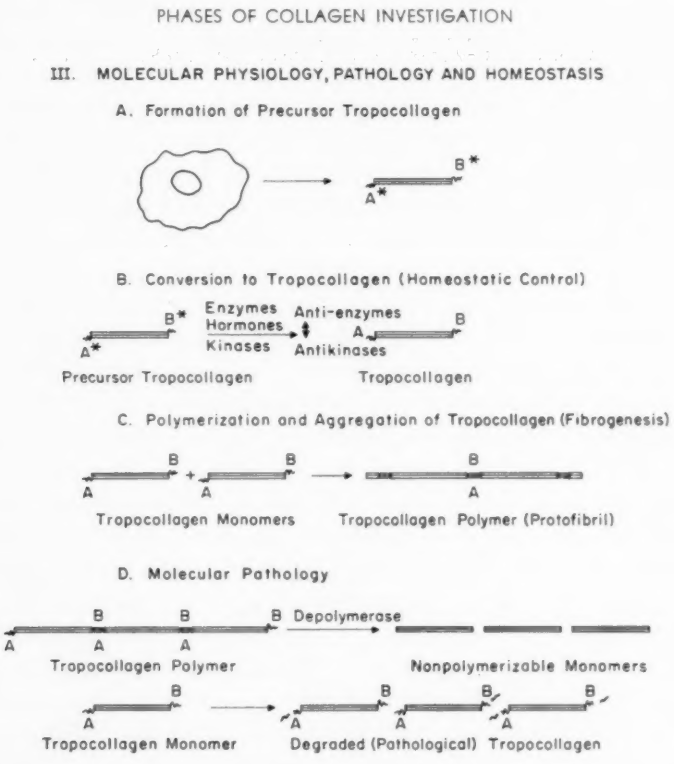


Fig. 5—Third (near future) phase of collagen investigation: molecular physiology, pathology, and homeostasis; characterization of enzymatic, hormonal, and ionic control mechanisms.

medical problems seem to get stalled in this first phase of descriptive morphology; the analyses may be sophisticated from the biophysical and biochemical viewpoint, but they do not lead to an understanding of the molecule itself. In the second phase (Figure 4) the macromolecular entity is isolated and its interaction properties, with molecules of its own kind and with other large and small molecules and with various factors in the chemical environment, are determined. The effective and creative development of the third, contemporaneous, phase (Figure 5), involving the quest for the control enzymes and cofactors, requires not only a good grasp of the vast literature of histology, physiology, biochemistry, and pathology, but also the ability to select from this vast

welter of information the leads that will prove most fruitful. The systems and partial systems in such homeostatic control mechanisms are unquestionably complex; all manner of immediate and remote "controls" must be devised to avoid being misled by correlations that are more apparent than real.

Professional Stabilization Needed

With the aid of a few case histories, I have attempted to document the critical importance of this level of investigation, which must be actively developed if the concepts and methods of the basic sciences are to be fruitfully applied in biomedical research. For competent, well-trained investigators to be attracted to such research, and to prove effective in it, requires a mental set strikingly different from that of the analytical scientist in the simpler "basic" fields of the life sciences, and also from that of the clinical scientist, whose investigations involve responsibility for the human beings the cure of whose ills is his primary interest. The manner in which he poses his questions and frames his strategic research plans is totally different from that of his colleagues at the "lower" and the "higher" levels. He must be aware of the content and of the new ideas in the basic biophysical and biochemical disciplines, yet he cannot afford to indulge in extensive inquiries into such "clean and decent" matters himself; his proper sphere is in the higher reaches of organizational complexity. He must be aware of the pressing problems of human disease and be warmly, if not passionately, desirous of contributing to the abolition of human suffering resulting from these diseases. Yet he dare not yield to the temptation of indulging in a superficial attack at the level of the whole organism by methods that are seldom better than pseudo-scientific.

In general, individuals attracted to this intermediate zone in the hierarchy of biomedical research have been trained in medicine and have received some years of postdoctoral training in the more basic fields of the natural and life sciences before settling down to careers of research in a medical school, hospital, or research institute. It is becoming fairly common to add a Ph.D. in biochemistry or biophysics to the M.D. To a lesser extent, individuals with professional training in biology, biochemistry, or biophysics find their way into the field.

Funds in fairly generous amounts and with long-term commitments are available from federal and private granting agencies to defray the

costs of biomedical research, including the salaries of the principal investigators. However, there is urgent need to provide adequate professional status and economic stability for those attempting to span the gap between basic science and clinical research. Frequently such individuals, gifted and productive though they may be, are not easily fitted into classically defined disciplines or departments of medical faculties. They cannot aspire to chairs or even tenure positions in clinical departments (except in those rare institutions which maintain departments of experimental medicine or experimental pathology) because they do not wish to undertake patient care or the teaching of clinical subjects. They do not fit into the programs of the natural sciences and philosophical faculties of universities because their competence and interests lie in areas of the life sciences that overlap and interdigitate with traditional university disciplines, but do not coincide sufficiently with these to meet the academic requirements in the teaching of established academic curricula. They are professional pioneers and as such wander far from the sheltered pools of established academic organization.

Such programs of applied molecular biomedical research are of incalculable value to teaching hospitals, particularly those which function as the clinical teaching service of medical schools and universities, which have strength in basic and preclinical science. Clinicians and clinical investigators gain much from easy contact with the staff of basic-research groups. The latter also profit greatly from the insight and experience of their clinical colleagues and from invaluable research material that may be obtained in hospitals.

Few teaching hospitals or medical schools can afford, in addition to all their other commitments, to support from endowed funds a substantial number of life-tenure appointments for such programs intermediate between basic and clinical research. However, if there is strong conviction of the intrinsic value of such work and of the synergistic role the investigators play in connection with the other two functions of the hospital—teaching and the care of the sick—ways can be found to meet the need. In the belief that the present strong financial support from governmental and granting agencies is not a temporary but a permanent program that is likely to be further increased in depth and scope, the Massachusetts General Hospital has recently committed itself to the establishment of a substantial number of life-tenure positions on its research staff. The cost of insuring such permanent positions can be

met by the establishment of a permanent fund from contributions of a small fraction of the professional salaries. It seems probable that this cost may also be assumed by governmental agencies as a proper cost of the operation, a kind of "intellectual overhead" given without strings to the institution to help provide essential stability. It goes without saying that in selecting investigators for such life-tenure appointments the same rigorous care must be exercised as is usual in the filling of university chairs.

Mention should also be made of the importance of encouraging, by whatever means may serve, the easy communication between research staff and the other professional hospital personnel. Failing this, the research staff may become segregated by a kind of professional coacervation, thus defeating the purpose for which the research center was established in the context of the teaching hospital.

The points we have attempted to make, aided by a few case histories, may be summarized as follows: In the attack on problems of molecular biology and molecular diseases, the molecules or macromolecules of interest must first be isolated and characterized as completely as possible. The biophysical and biochemical sophistication required for this is frequently such as to make its prosecution most profitable in a university department or laboratory of basic science. But even complete success in characterizing the molecule of interest constitutes only the first phase of the campaign. This must be followed by a study of the homeostatic mechanisms by which the molecule is synthesized, modified, and adapted to the needs of the organism and of the alterations of the system that produce disease. Without the second phase the triumphs of molecular biology will be meaningless to the clinician and to the patient. The second phase, requiring an interdisciplinary approach, involves considerable postdoctoral training. In spite of this formidable obstacle, an evergrowing pool of dedicated investigators exists. However, scant provision has been made to assure these investigators professional status and economic stability. One reason for this is that the investigations cut across traditionally established lines of academic departments. There are few departments or professorships of molecular biomedical research. A few institutions are meeting the problem by establishing a substantial number of life-tenure appointments, every safeguard being taken to assure the highest quality of appointees. If the large costs of the total program, supported primarily by governmental

and granting agencies, are justified, as we fully believe, then the relatively small additional cost of this contribution to institutional stability through tenure appointments to a limited number of highly competent investigators is fully warranted, and would do much to ensure the uninterrupted flow of information from the basic level of the molecule to the clinical level of the patient.

REFERENCES

1. *Biophysical science—a study program.* J. L. Oncley, edit. New York, John Wiley & Sons, Inc., 1959.
2. Levene, P. A. and Bass, L. W. Nucleic acids, *Amer. chem. Soc. Monogr. Ser.* New York, Chem. Catalog Co., 1931.
3. Herzog, R. O. and Jancke, W. J. Verwendung von Röntgenstrahlen zur Untersuchung metamikroskopischer biologischer Strukturen, in *Festschr. Kaiser Wilhelm Ges. Förd. Wiss. 10-jähriges Jubiläum.* Berlin, 1921, pp. 118-20.
4. Meyer, K. H. and Mark, H. *Der Aufbau der hochpolymeren organischen Naturstoffe.* Leipzig, 1930.
5. Astbury, W. T. *Fundamentals of fibre structure.* Oxford, 1933.
6. Franklin, R. E. and Gosling, R. G. Molecular configuration in sodium thymonucleate, *Nature 171:*740-41, 1953.
7. Wilkins, M. H. F., Stokes, A. R. and Wilson, H. R. Molecular structure of deoxypentose nucleic acids, *Nature 171:* 738-40, 1953.
8. Crick, F. H. C. and Watson, J. D. Complementary structure of deoxyribonucleic acid, *Proc. roy. Soc. A 223:*80-96, 1954.
9. Meselson, M. and Stahl, F. W. Replication of DNA in *Escherichia coli, Proc. nat. Acad. Sci. 44:*671-82, 1958.
10. Perutz, M. F. Some recent advances in molecular biology, *Endeavour 17:*190-203, 1958.
11. Horsfall, F. L., Jr. Can viruses be managed? *Proc. Amer. phil. Soc. 102:* 442-47, 1958.
12. Avery, O. T., Macleod, C. M. and McCarty, M. Studies on the chemical nature of the substance inducing transformation of pneumococcal types, *J. exp. Med. 79:*137-58, 1944.
13. Furth, J. and Metcalf, D. Appraisal of tumor-virus problems, *J. chron. Dis. 8:*88-112, 1958.
14. Kendrew, J. C. and associates. Structure of myoglobin, *Nature 185:*422-27, 1960.
15. Perutz, M. F. and associates. Structure of haemoglobin, *Nature 185:*416-22, 1960.
16. Hall, C. E. Method for the observation of macromolecules with the electron microscope illustrated with micrographs of DNA, *J. biophys. biochem. Cytol. 2:* 625-28, 1956.
17. Hall, C. E. and Doty, P. Comparison between the dimensions of some macromolecules determined by electron microscopy and by physical chemical methods, *J. Amer. chem. Soc. 80:*1269-74, 1958.
18. Sanger, F. Structure of insulin, in *Currents in biochemical research.* D. E. Green, edit. New York, Interscience Publ. Inc., 1956, pp. 434-59.
19. Ingram, V. M. Chemistry of the abnormal human haemoglobins, *British med. Bull. 15:*27-32, 1959.
20. Pauling, L. Hemoglobin molecule in health and disease, *Proc. Amer. phil. Soc. 96:*556-65, 1952.
21. Pauling, L. Abnormality of hemoglobin molecules in hereditary hemolytic anemias, *Harvey Lectures, Ser. 49,* 1953-1954, pp. 216-41.
22. Waugh, D. F. Blood coagulation—a study in homeostasis, in *Biophysical science—a study program.* J. L. Oncley, edit. New York, John Wiley & Sons, Inc., 1959, pp. 557-62.
23. Bailey, K., Astbury, W. T. and Rudall,

K. M. Fibrinogen and fibrin as members of the keratin-myosin group, *Nature 151*:716-17, 1943.

24. Hawn, C. V. Z. and Porter, K. R. Fine structure of clots formed from purified fibrinogen and thrombin: a study with the electron microscope, *J. exp. Med. 86*:285-92, 1947.
25. Hall, C. E. Electron microscopy of fibrinogen and fibrin, *J. biol. Chem. 179*:857-64, 1949.
26. Hall, C. E. and Slayter, H. S. Fibrinogen molecule: its size, shape, and mode of polymerization, *J. biophys. biochem. Cytol. 5*:11-16, 1959.
27. Astbury, W. T. Molecular structure of the fibres of the collagen group, *J. int. Soc. Leath. Chem. 24*:69-91, 1940.
28. Bear, R. S. Structure of collagen fibrils, *Advanc. Protein Chem. 7*:69-160, 1952.
29. Schmitt, F. O., Hall, C. E. and Jakus, M. A. Electron microscope investigations of the structure of collagen, *J. cell. comp. Physiol. 20*:11-33, 1942.
30. Kühn, K., Grassmann, W. and Hoffmann, U. Die elektronmikroskopische "Anfärbung" des Kollagens und die Ausbildung einer hochunterteilten Querstreifung, *Z. Naturf. 13*:154-60, 1958.
31. Kühn, K. Über die Ausbildung einer hochunterteilten Querstreifung des Kollagens nach Gerben mit Phosphowulframsäure und basischer Chromsalzlösung, *Das Leder 9*:217-22, 1958.
32. Rich, A. and Crick, F. H. C. Structure of collagen, in *Recent advances in gelatin and glue research*. G. Stainsby, edit. New York, Pergamon Press, 1958, pp. 20-24.
33. Orekhovitch, V. N., Tustanowski, A. A., Orekhovitch, K. D. and Plotnikova, N. E. Procollagen of hide, *Biokhimija 13*:55-60, 1948.
34. Highberger, J. H., Gross, J. and Schmitt, F. O. Interaction of mucoprotein with soluble collagen: an electron microscope study, *Proc. nat. Acad. Sci. 37*:286-91, 1951.
35. Gross, J., Highberger, J. H. and Schmitt, F. O. Collagen structures considered as states of aggregation of a kinetic unit. The tropocollagen particle, *Proc. nat. Acad. Sci. 40*:679-88, 1954.
36. Hodge, A. J. and Schmitt, F. O. Charge profile of the tropocollagen macromolecule and the packing arrangement in native-type collagen fibrils, *Proc. nat. Acad. Sci. 46*:186-97, 1960.
37. Schmitt, F. O., Gross, J. and Highberger, J. H. Tropocollagen and the properties of fibrous collagen, *Exp. Cell Res. (Suppl. 3)*: 326-34, 1955.
38. Boedtker, H. and Doty, P. Native and denatured states of soluble collagen, *J. Amer. chem. Soc. 78*:4267-80, 1956.
39. Hall, C. E. Visualization of individual macromolecules with the electron microscope, *Proc. nat. Acad. Sci. 42*:801-06, 1956.
40. Hodge, A. J. and Schmitt, F. O. Interaction properties of sonically fragmented collagen macromolecules, *Proc. nat. Acad. Sci. 44*:418-24, 1958.
41. Hodge, A. J., Highberger, J. H., Deffner, G. G. J. and Schmitt, F. O. Effects of proteases on the tropocollagen macromolecule and on its aggregation properties, *Proc. nat. Acad. Sci. 46*:197-206, 1960.
42. Gross, J., Highberger, J. H. and Schmitt, F. O. Extraction of collagen from connective tissue by neutral salt solutions, *Proc. nat. Acad. Sci. 41*:1-7, 1955.
43. Gross, J. On the significance of the soluble collagens, in *Connective tissue, thrombosis and atherosclerosis*. I. H. Page, edit. New York, Academic Press, 1959, pp. 77-95.
44. Levene, C. I. and Gross, J. Alterations in state of molecular aggregation of collagen induced in chick embryos by β-aminopropionitrile (lathyrus factor), *J. exp. Med. 110*:771-90, 1959.
45. Randall, J. T. Observations on the collagen system, *J. int. Soc. Leath. Chem. 38*:362-87, 1954.
46. Bear, R. S., Bolduan, O. E. A. and Salo, T. P. Model for collagen fibril structure derived from small-angle x-ray diffraction, *J. Amer. Leath. Chem. Assoc. 46*:107-23, 1951.

RECENT OBSERVATIONS ON THE LEWIS SYSTEM*

PHILIP LEVINE

Director, Division of Immunohematology, Ortho Research Foundation, Raritan, New Jersey

IN ADDITION to hereditary variations that occur in individual proteins of human serum, there is another hereditary** property of normal serum which is probably a polysaccharide bound to a glycoprotein. I am referring to the soluble Lewis substances in human plasma and analogous substances in animal plasma—J substance in cattle and R substance in sheep. Characterization of these materials as glycoproteins is based on studies of J substance in beef plasma by Bednekoff *et al.*[1] The substances in human saliva which have inhibitory characteristics are similar to plasma mucopolysaccharides. Finer biochemical studies of these substances were carried out by Annison and Morgan[2], using pseudomucinous ovarian cyst fluid, which is rich in blood group substance. Saliva contains larger quantities of Lewis substances than does plasma. The Lewis substance, Le^a, is present in largest amounts in those individuals who are nonsecretors of ABH substances. The Lewis story cannot be told without referring to another substance, Le^b, which is closely associated with the H substance found in all secretors of ABH. Only individuals whose red cells are of type Le(a–b–) fail to secrete any Lewis substances.

The heredity of the Lewis property can be understood only if one considers secretion of the substance in saliva rather than agglutination reactions of red cells. As will be shown below, the reactions of red cells with anti-Le^a and anti-Le^b are secondary effects resulting from their exposure to plasma containing the substances. The story is a complicated one and there are a number of theories. Available evidence supports the views of Grubb[3] and Ceppellini[4] that ABH and Le^a secretion are genetically independent, but some interaction must occur in order to explain

* Presented at the meeting of the Section on Microbiology, The New York Academy of Medicine, November 12, 1959.

**Reference is made here to the preceding paper delivered at the same meeting by Dr. Oliver Smithies, Connaught Medical Research Laboratories, University of Toronto, Canada.

TABLE I—PHENOTYPES
MODIFIED AFTER CEPPELLINI — SCHEME OF THE LEWIS SYSTEM AND SECRETION OF ABH*

	Saliva			*Red Cells*
	ABH	Le^a	Le^b	
SeSe LL SeSe Ll Sese LL Sese Ll	+	+	++	Le(a—b+)
sese LL sese Ll	o	++	o	Le(a+b—)
SeSe ll Sese ll	++	o	o**	Le(a—b—)
sese ll	o	o	o	

**with selected sera.

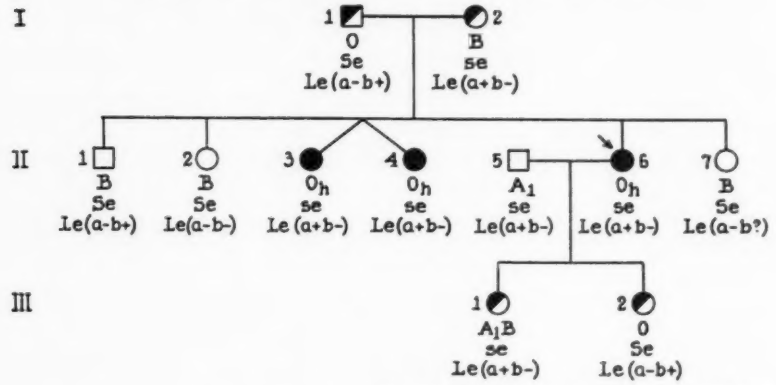
Se and se represent genes for secretion and nonsecretion of ABH.
L and l represent genes for secretion and nonsecretion of Le^a.

* By permission of the authors, R. R. Race and R. Sanger, Blood Group Research Unit, The Lister Institute, London, England. By permission of the publisher, C. C Thomas, Springfield, Ill.

why more Le^a substance is produced by nonsecretors of ABH. These findings are summarized in Table I.

This theory is strongly supported by several examples of the so-called "Bombay" blood, which is characterized by suppression of ABH antigens on the red cells and in the secretions. All bloods tested—more than a dozen—were shown to be Le(a+). Genetically, these findings can best be explained by a suppressor gene, *x*, at an independent locus, which (when homozygous) suppresses production of ABH on the red cell and in the secretions. Blood group substrate is thus available only for production of Le^a substance. In the family presented in Figure 1, which I studied several years ago[5], blood group B and salivary secretions of B and H are suppressed by *xx*.

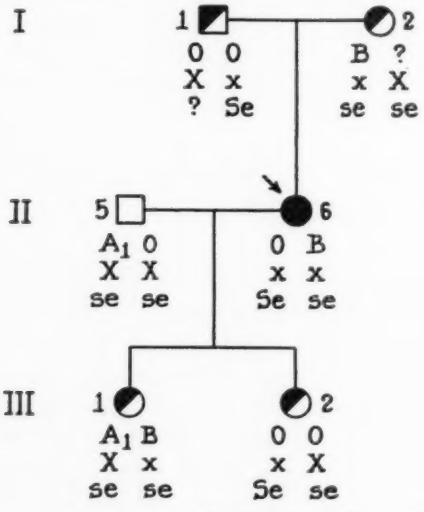
THE BOMBAY TYPE OF FAMILY OF LEVINE *ET AL.*[5]



By permission of Grune & Stratton, Inc., publishers

Fig. 1. complete shading = homozygous for rare gene
partial shading = heterozygous for rare gene
Se: secretor of ABH substances
se: nonsecretor of ABH substances
The blood of II-7 was not tested with anti-Le^b

ABO, SECRETION AND SUPPRESSOR GENOTYPES IN THE BOMBAY TYPE OF FAMILY OF LEVINE *ET AL.*[5]



By permission of Grune & Stratton, Inc., publishers

Fig. 2. The schematic arrangement of the genes as given above does not imply linkage. In the propositus, II-6, the blood factor B and secretion are suppressed in the phenotype so that the blood behaves like a group O and the individual appears to be a nonsecretor.

The phenotypic mating in Generation II, shown in Figure 2, A nonsecretor by apparent O nonsecretor, results in what appear to be two violations of the rules of heredity. But the appearance of factor B in the group AB in III-1, and secretion in the group O, III-2, can be readily explained on the basis of suppression by two doses of the suppressor gene *x* in the propositus and the failure to suppress when *xx* segregates in Generation III. The unusual property in the blood of the propositus termed by the author as O_h is most readily recognized by the presence in the serum of anti-H as well as anti-A and anti-B.

I should now like to refer to several lines of evidence which support the view that the three types of Lewis reactions given by red blood cells are artefacts resulting from exposure to Lewis substances in their own plasma. This had already been shown for the J substance in cattle blood by Stormont as far back as 1949[6].

In 1955 Sneath and Sneath[7] succeeded in transforming Le(a–) red cells to Le(a+) by exposure to Lewis-containing plasma. These findings are summarized in Table II.

TABLE II—*IN VITRO* TRANSFORMATION OF THE LEWIS RED CELL PHENOTYPE WITH PLASMA—AFTER SNEATH AND SNEATH[7]

	Red Cells		
Plasma	Le(a+b–)	Le(a–b+)	Le(a–b–)
Le(a+b–)	—	Le(a+b+)	Le(a+b–)
Le(a–b+)	Le(a+b+)	—	Le(a–b+)
Le(a–b–)	Le(a+b–)	Le(a–b+)	—

Remarkably enough, this transformation could not be induced by exposure of normal red cells to saliva, which is far richer in soluble Lewis substances. However, we succeeded recently[8] in transforming Le(a–b+) red cells to Le(a+) by employing the tanned red cell method of Boyden[9] (Table III).

It is beyond the scope of this paper to speculate on the changes induced in the red cell by exposure to tannic acid. Suffice it to say that

TABLE III—*IN VITRO* TRANSFORMATION OF TANNED Le(a—b+) RED CELL WITH SALIVA

Le(a—b+)	*Number of Saliva Specimens Tested*	*Anti-Le^a*
Tanned only	11	0
Tanned & coated with saliva		
Le(a+b—)	4	++ — +++
Le(a—b+)	2	+ — ++
Le(a—b—)	5	0
Control red cell Le(a+b—)		++++

only minute quantities of Le^a substance in the saliva become fixed to the tanned red cell, and that the saliva when coated onto tanned rabbit red cells produces saline-agglutinating anti-Le^a in the rabbit.

The transformation by plasma could also be demonstrated in transfusing a patient possessing Le(a—b+) with Le(a+b—) blood. On separating donor Le(a+) red cells by differential Rh agglutination, the bloods differing in some Rh antigens, we noted that the transfused donor's red cells had become Le(a+b+). The donor's red cells must have absorbed Le^b substance from the recipient's plasma. But the most convincing experiment on transformation was carried out by nature in the rare human chimeras resulting from placental anastomosis in twin pregnancies. Of the three such examples reported in the literature, the twin cases of Nicholas, Jenkins and Marsh[10] differed in several blood group antigens and also in their Lewis reactions (Table IV).

Thus, Twin 1, whose blood (group O) contained 51 per cent of his co-twin's group A, Ns/Ns and R^2R^2 red cells, did not retain the Le(a+b—) red cells of the latter. Instead, they were transformed to the host's Le(a—b+). The host group O twin failed to produce anti-A. Similarly, Twin 2 was Le(a+b—) and his plasma converted the co-twin's Le(a—b+) red cells to conform to his own Le(a+b—) type.

Within the limits of the time allotted to me, it is not possible to refer to the several other theories on the heredity of the Lewis system

TABLE IV—CHIMERA FAMILY OF NICHOLAS, JENKINS & MARSH[10]
TRANSFORMATION OF LEWIS REACTIONS

Twin 1 — Host	*Co-twin*	*Twin 2 — Host*	*Co-twin*
49	51	61	39
O	A	A	O
Anti-B		Anti-B	
Ms/Ns	Ns/Ns	Ns/Ns	Ms/Ns
R^2r	R^2R^2	R^2R^2	R^2r
Le(a—b+)	Le(a—b+)	Le(a+b—)	Le(a+b—)
Se(H)		se	
L1		LL or L1	

which are briefly reviewed elsewhere[11]. The subject is very complex; and in closing I should like to quote from Race and Sanger, who write as follows: "Pettenkofer has a theory but it is in German and it beats us. Lewis theories are difficult enough in English!"

REFERENCES

1. Bednekoff, A. G. and others. Chemical studies on the J substance of cattle serum, *Proc. X Int. Congr. Genet. (abstr.) 2*:19, 1958.
2. Annison, E. F. and Morgan, W. T. J. Lewis (Le^a) human blood-group substance, *Biochem. J. 49*:xxiv, 1951.
3. Grubb, R. Observations on the human group system Lewis, *Acta path. microbiol. scand. 28*:61-81, 1951.
4. Ceppellini, R. On the genetics of secretor and Lewis characters: a family study, *Proc. Vth Int. Congr. Blood Transf., Paris*, 207-11, 1955.
5. Levine, P. and others. Gene interaction resulting in suppression of blood group substance B, *Blood 10*:1100-08, 1955.
6. Stormont, C. Acquisition of the J substance by the bovine erythrocyte, *Proc. nat. Acad. Sci., Wash. 35*:232-37, 1949.
7. Sneath, J. S. and Sneath, P. H. A. Transformation of the *Lewis* groups of human red cells, *Nature 176*:172, 1955.
8. Levine, P. and Celano, M. Antigenicity of Lewis (Le^a) substance in saliva coated onto tanned red cells, *Vox Sang.* In press.
9. Boyden, S. V. Adsorption of proteins on erythrocytes treated with tannic acid and subsequent hemagglutination by anti-protein sera, *J. exp. Med. 93*: 107-20, 1951.
10. Nicholas, J. W., Jenkins, W. J. and Marsh, W. L. Human blood chimeras, study of surviving twins, *Brit. med. J. 1*:1458-60, 1957.
11. Race, R. R. and Sanger, R. *Blood groups in man.* Springfield, Ill., C. C. Thomas, 1958, 3rd ed., pp. 200-14.

CHALLENGES IN A CHANGING WORLD*

H. D. KRUSE

Executive Secretary, Committee on Public Health,
The New York Academy of Medicine

TWO TRANSCONTINENTAL TRAINS bound in opposite directions stopped on adjacent tracks of a station in the middle west. Passengers from both trains used the same platform for an interlude of walking. Unexpectedly, one man from New York met a friend from Los Angeles who suggested that they talk over old times in the club car of his train. About 20 minutes later one of them became conscious that the car was moving. So impressed was he by the marvel of what was apparently happening that he exclaimed: "Ain't science wonderful? Here you are going to Los Angeles and I am headed for New York and we are both on the same train."

It is possible to draw several lessons from this story but I shall content myself with one: ain't science wonderful? Whether it be in the realm of the very large or the very small, could any other age claim such a dazzling and spectacular succession of achievements? New techniques have greatly extended man's observations and speculation in astronomy. I have read and reread the hypothesis of an ever-expanding universe and it is still almost beyond comprehension. No less overwhelming is the latest thought on the creation of the earth. This colossal convulsion is now viewed as a series of chemical and physical reactions which has even been repeated on a model scale in the laboratory. It must have been an astounding and awe-inspiring spectacle. But these are not man's accomplishments; rather they are instances of his new and larger understanding of nature's mysteries. On the still wonderful but lesser level of man-made events may be mentioned the successful orbiting of satellites. At this moment nine man-made satellites are zooming over us in outer space. Now for the first time we may even look at photographs of the far side of the moon. And men are being readied for a thrilling and adventurous trip to that planet.

Man's conquest of the very small has been no less overwhelming.

* Presented to the Committee on Public Health on January 4, 1960.

It is sufficient to point out that this is called the atomic age, sometimes the electronic age. We have atom-powered submarines and atom bombs because man learned to penetrate the atom, to use fusion and fission in discovering the structure of the atom in its manifold minute parts. No longer is it sufficient to know that molecules are composed of atoms. By latest count physicists have identified 30 distinctly different elementary particles. On the applied side, automation, under the guidance and control of electronics, seems to be not only taking over more and more of man's monotonous and tedious tasks, but also performing many superhuman functions.

Moving along with this surging wave of advance, biology and medicine have also had their triumphs. Tagged atoms in the form of radioactive isotopes have revealed many of nature's deepest metabolic secrets. By the electron microscope the kingdom of viruses has become visible. It seems only yesterday that P. A. Levine and Walter Jones were starting to work on nucleic acids, more with hope than with promise, while chromosomes were demonstrable but not observable. Today chemists draw diagrams of the chromosomes, the arrangement of the genes in them, and have succeeded in synthesizing the nucleotides that are believed to be the transmitters of hereditary qualities.

Even our social and cultural pattern has changed profoundly in our lifetime. Scarcely any part of living has gone unaltered. Most of us have adapted so successfully to the new way of life that we hardly realize the veritable revolution through which we have lived. We are content to have occasional moments of reminiscence when we briefly recognize what we euphemistically call the passing of an era. Keeping pace with the time, the practice of medicine is not exactly as it was in the "horse and buggy days". *Medicine and the Changing Order*, the Academy has called it, in recognition that the most constant fact of life is change. Much of it has been for the better, at least we have so convinced ourselves.

But we also have our moments of doubt whether our new world is a veritable Paradise. After all, the social body, like the human body, has the potential not only for growth and maturation, but also for development of disorders. At present, signs indicative of social ills seem to be discernible. First, to some persons, despite all the wonders of our modern living, these are troubled times. Several lines of evidence to substantiate this point might be developed, but it is sufficient to cite the

present magnitude of juvenile delinquency, drug addiction, alcoholism, and use of tranquilizers. Secondly, there seems to be an outcropping of deception associated with avarice, greed, and outright venality. Rigged TV quizzes, plugs for sale, cheating in the butcher shops, irregularities in granting drivers' licenses, misleading advertising, and peddling of influence for a price are in the headlines. Grand Juries and Congressional Committees are busy on one or another of these improprieties, if not illegalities. New words have appeared to describe the alleged indiscretions: payola, kickback, fast buck. Directly or indirectly, at the core of all these sharp practices is the timeless interplay of ethics and economics. In question is whether man's moral development has kept pace with the tremendous new power, wealth, and leisure which his technical success has brought him.

There is nothing fundamentally new or unique in this situation. In one form or another it has always been with us. The form, the names, the places, the circumstances change, but the basic situation is the same—man's greed. In his time Cicero complained bitterly about the corruption in Roman life. In the pages of history of every age may be found similar Jeremiads. Remember Teapot Dome, mink coats, and ten percenters? This incomplete recital of the bad of our times is not meant to convey that this is the first and lowest point in trouble and wickedness. But to say that evil is not new and is always with us is not to say that it is not worse at one time or another. Periodically it shows exacerbation. There is no accurate meter to measure the degree of dullness on the edge of ethics. But the volume, intensity, and variety of the outcry may be some indication of its magnitude and severity. To take just one example, a full, double-page advertisement in *The New York Times* was taken recently to point out that the hanky-panky in TV is only a symptom of general lowering of ethics today.

Not all the disturbing and controversial aspects of contemporary life are improprieties. During the past five years there has been evidence of anxiousness and concern over the present-day system of education. Amidst the crescendo of criticism and rebuttal, organizations have been formed, books published, articles and letters to the editor written, either attacking or defending, blaming or extolling modern education. Without discussing the merits of the arguments on both sides, it is pertinent to ask whether any generation has been completely satisfied with its principles and practices of education. Here is one comment: "There is

now less flogging in our great schools than formerly but then less is learned there." That might have been taken from today's paper. Actually, it was an utterance by Dr. Samuel Johnson. Even medical education has been under scrutiny and modification. Tinkering with the curriculum, either actual or proposed, has been a steady business for a number of years. Regardless of opinions whether there has been gain or loss, it is a fact that the whole concept of education of the medical student and young physician is today quite different than it was several decades ago. This is equally true of nurses' training. Changes have occurred; yet there are problems.

This sketchy description of our world at present, the good with the bad, the satisfying with the troublesome, is drawn to depict the setting in which the Committee on Public Health must carry on its mission. For it is upon the Committee, its nature, responsibility, and work that I would focus attention. Out of its several significant characteristics, three should be emphasized. First is its singularity. In this day and age it is regarded as unique that there is such a group of practicing physicians, guardians of personal health, who deliberate upon public health policy and practice. So far as I know, there is no other group exactly like it. It is unfortunate that such social interest is not associated in the public mind today with the medical profession. True, such a group is rare, but it is not new. Rather, it is one of the good customs retained from the past. Then physicians participated not infrequently in politics, government, and social action. After all, several were signers of the Declaration of Independence. As might be expected, an even greater number were active in behalf of the public health of those days. I suppose that the less close linkage of the clinician with public health through the years has been the inevitable consequence of specialization. With the development of public health practice as a separate field with its own roster of professionals and its separation from the practice of medicine, the association between the two groups assumed a new and less intimate relationship. Yet in the long run, both groups have the same goal. Indeed, it is sometimes difficult to draw a line between clinical medicine and public health. Recognizing the continued responsibility of medicine in public health, this Committee has maintained the traditionally active role with adjustment to the times. In his book *Aristocracy in America*, appearing in 1835, Francis J. Grund, a naturalized citizen, described what distinguishes a true aristocrat: "A sense of responsibility

and an effort to protect members of the so-called lower order." Some words in this definition are not in use today. The thought would be more suitably phrased if "fellow man" were substituted for "lower order". But I can think of no more succinct explanation for the uniqueness of this Committee.

The second characteristic of this Committee is its integrity. At first sight it may seem gratuitous to commend a group for its honesty. But it is no secret to psychologists and students of human nature that man possesses a trait called "self-interest". When this trait is inhibited or repressed or when it is embarrassing for it to be recognized, it is said to go underground in the subconscious. I recall a notice on the bulletin board of a church, "Closed for the summer". Ironically, appearing just beneath it was the thought for the day: "The devil never sleeps." In full cognizance of human frailties, it is my opinion that through the years this Committee has manifested a minimum of self-interest or its equally obnoxious relation, conflicting interest. Truly, this band of men has been as little self-serving as is humanly possible. So conspicuous has been its reputation for integrity that it has become a tradition which pervades the very air of its meeting hall.

Closely akin to the second characteristic of the Committee is the third—its spirit of independence in thought and action. One of the greatest obstacles to clear and logical thinking for public good is self-interest. Once that barrier is removed, the chances of obtaining superior judgment are enhanced. This Committee has a praiseworthy record of thinking independently, speaking its mind, and taking leadership in action. Too often, all around us, independent thinking is praised in principle and shunned in practice. In a day when straight thinking, plain speaking, and forthright action violate the prevailing code of Carnegie, Dale, that is, it is inspiring to witness a group that is committed solely to the search for truth in the maintenance of public health.

These qualities of integrity and independence are in large part responsible for the Committee's remarkable record over a span of nearly 50 years. Several years ago, in describing the work of the Committee, I classified the types of problems on the basis of finality of solution. Perhaps the most challenging, exacting, and important category comprised so-called perennial problems. Their distinguishing characteristic was the continuance or re-development of difficulty. Usually they had been long-standing issues with lengthy and complex histories and a train

of accumulated difficulties; hence, they were not basically new. Again and again they recurred, but each time the names, the circumstances, the occasion, and the situation were different. Such an issue seemed to form a never-ending continuum with a succession of incidents.

In pondering over the reasons for the persistence of these recurring problems, I was struck by their similar histories. Whether it be through a period of progress, standstill, or decline, the march of time creates problems or aggravates existing difficulties. Social changes, whether planned or unplanned, even when they are judged to be advances, are accompanied by unexpected and sometimes undesired, as well as beneficial effects. Little seems to be all white or even grey. In the parlance of the day, the outcome appears in living color. It almost seems that the remedies and solutions applied to these problems carry the seeds of new difficulties, or the same difficulties in a new guise. Sometimes one situation is improved at the expense of another.

To be realistic, there appear to be matters which are never finally, completely, and permanently settled. Indeed, few solutions can lay claim to perfection. Eternal vigilance seems to be necessary. Many of the problems in the perennial category have been inherited from the past with all the accumulated ills of years and with fixed, entrenched positions and opinions on all sides. Such a situation makes a logical, simple, and permanent solution difficult. It would be much easier to start *de novo* than to change an established situation. But the interests are often so large, so important, and have existed so long that any solution threatening their autonomy or *modus operandi* is apt to be opposed and resisted. In the face of such realities, the solution is almost never neat and simple, nor may it be enduring. It is much like the plight of a Professor of Economics who admitted that he had given the same set of questions in final examinations each year for the past 15 years. "But", he explained, "the answers change every year."

In recent years the Committee has addressed itself to a series of important problems: drug addiction, barbiturates, tranquilizers, hepatitis, fluoridation, collection, processing and distribution of blood, psychiatric clinics, and air pollution. Each topic in this list is sufficiently important to merit a comprehensive discussion. But surely there would be little real enjoyment for you to listen to a retelling of events in which you participated. It is sufficient to note four points: 1) There were ethical, economic, or educational considerations in these topics; 2) some of the

matters were of the hardy perennial type; 3) in each instance the Committee formulated constructive recommendations that gave promise of effectiveness; 4) it displayed integrity and independence in reaching its decisions. Sometimes its views ran counter to the prevailing opinion. Yet it never hesitated to stand virtually alone in its position.

Now the Committee is in the midst of examining the present system of pharmaceutical advertising to physicians, particularly in the promotion of new drugs. Here is a subject with all three aspects: ethics, economics, and education. This topic came to the Committee's attention several years ago in the course of its deliberations on the overuse and misuse of tranquilizers. It should be noted that in its concern over present practices in advertising to physicians the Committee is not alone. At least one medical journal has been conducting a sustained crusade through its editorial columns. Others are now joining in the chorus. Here is an opportunity for the Committee to employ its talent in order to bring improvement.

What are some of the outstanding problems that are a challenge today? Perhaps the most immediately pressing problems that are most significantly related to the health of the public are in our own territory. All is not well there. Surely this situation has not gone unobserved by members of the medical profession.

Without attempting to specify all the areas in which difficulties exist, five may be readily enumerated:

First, many hospitals are in economic difficulties. This is common knowledge, for the hospitals have divulged their financial position to the public. This is an old story but the situation appears to be particularly acute at the present time.

The next two problems are presented separately, although it is the hospitals again that are most affected. One of these difficulties is the shortage in nursing staff. This is a subject about which the Committee on Public Health has been concerned for a number of years and to which it has made at least one substantial contribution after endless hours of frustrating conferences. The New York County Medical Society has just issued a report on the subject which is an extremely thoughtful and constructive document. But the shortage still exists and affects most of the hospitals.

The third problem, distribution of interns, differs from the preceding in that only some of the hospitals feel its effects. The line is rather

sharply divided between the haves and have nots. But it is an elementary observation that inequalities create an unstable system, which is not the most desirable state.

Fourthly, there is the fantastically increasing rate of malpractice suits. This development has reached the stage where it influences the practice of medicine and the cost of medical care. In addition, it brings in an oblique way an unwarranted slander of many professional reputations which in the long run may well impair the effectiveness of the whole profession. Judged by any reasonable standard, it is inconceivable that there could be so much faulty practice of medicine as might be concluded from the number of suits for action. A combination of give-away juries and contingency-fee lawyers seems to have brought the practice of medicine to this pass.

Fifthly, from time to time there are public expressions of dissatisfaction with the present general practitioner. The complaint may be summed up in the words, "he ain't what he used to be". But as Dizzy Dean so sagely observed, "Who is?"

Some of these problems grow more acute each year. The word "crisis" is heard more and more frequently. Hence there is an awareness of existing difficulties; indeed, there are many utterances in public and private that something ought to be done. But thus far matters seem not to have progressed beyond the talking stage.

Grave as some of these problems are, I shall resolutely repress my urge to discuss them in more detail. In passing, however, it may be noted that common reasons for these predicaments are: means confused with ends; conflicting objectives; and partisan interests. In each problem more than one interest is to be served. If one interest is made paramount and the ultimate and common goal is thereby obscured, the resulting imbalance is likely to prove troublesome. To add to the complexity, these problems have ethical, economic, and educational issues. It is said that Gertrude Stein's next to last words were, "What is the answer?" In a moment came her last words: "In that case, what is the question?" It is not improbable that if the right questions were asked, the right answers might be forthcoming. And the remedy would not necessarily be the same for each difficulty, nor do I believe that money would be the sovereign cure.

Many of these problems were once the concern of the Committee on Public Health until new organizations relieved them of those re-

sponsibilities. For that reason, they may be regarded technically as outside the Committee's sphere of activity. However, it is not impossible that in some of these problems the Committee may be brought back ultimately, if only temporarily, into former areas of action. From long experience, the Committee has found that to be most effective in its action the circumstances must be auspicious. And here opportunity and timing are decisive influences.

In this rapid sketch of our times it has been pointed out that we are living in a rapidly changing world with both good and bad features. Interwoven in its foremost problems are the very old and recurring considerations of ethics, economics, and education. To meet these problems, the answers of yesterday are not always adequate for today. But it is certain that the age-old qualities of integrity and independence are ever-essential ingredients. Those two words, integrity and independence, might be designated as the trademark of the Committee on Public Health. In 1911 it came into being to meet a need. Since then its services have continued to be in demand as new and different problems of each period have called for its clear and balanced judgment. Today, almost a half-century later, the problems are just as pressing and the qualities that characterize the Committee are as much needed as at any time in the past.

THE EARLY DIRECTORS OF THE MEDICAL SERVICES OF THE AMERICAN REVOLUTIONARY ARMY

LAURENCE FARMER

Attending Physician, Lenox Hill Hospital, New York, N. Y.

SHORTLY after assuming command of the troops encamped before Boston, General Washington informed Congress that he was greatly concerned about the army's medical establishment[1]. He had found it without over-all direction, without coordination of effort. In measured terms he had spoken of its "very unsettled condition". Torn as it was by quarrels, rivalries and dissension, with the surgeons at one another's throats, he could, without exaggeration, have called the situation chaotic.

With the troops that had hurriedly assembled in the environs of Boston after the encounters at Lexington and Concord, there had come a considerable number of doctors. These men, who were attached to individual regiments, had brought with them their own few medicines and surgical instruments and had established, in barns and sheds, what they euphemistically called "regimental hospitals". Since it soon became evident that these "hospitals" could not provide adequate medical care, the Massachusetts Provincial Congress established other, better equipped units that were placed under the direction of its own appointees. The regimental surgeons were up in arms. They were in no mood to relinquish the care of their patients to the larger hospitals as poorly equipped as their own were. They were not going to be pushed aside; they would demand equal consideration.

In response to the Commander-in-Chief's urgent request that Congress give this untenable situation its immediate attention, legislation was enacted establishing a medical department for the army[2]. This legislation made provision for the appointment of a "Director-General and Chief Physician" who was to head the department, and whom it invested with great authority and responsibility. It determined the number of surgeons and other personnel to be employed in the department and it called upon the Director-General to furnish "medicines, bedding

and all other necessaries . . . [and] to superintend the whole". For some inconceivable reason, the act made no provisions for the regimental surgeons. It took no cognizance of their grievances. It did not determine from where they were to receive supplies. It ignored their very existence. By its omissions it created conditions which were perennially to plague the Director-General and which more than once almost wrecked the medical department.

The man unanimously elected by Congress to head the new department, Dr. Benjamin Church, seemed eminently suited to iron out the disputes that had arisen in the ranks of the medical men. He was not only a leading physician but a tried patriot who stood high in the councils of the revolutionaries. He was a member of the Massachusetts Provincial Congress and of the Massachusetts Committee of Safety, and he was widely known as the man who had delivered the oration commemorating the fifth anniversary of the Boston Massacre. His antecedents made him appear as the ideal arbiter.

However, from the very beginning, Church was faced with obstacles beyond his control. By neglecting to integrate the regimental surgeons within the medical department, Congress had, unwittingly, created two medical services, each competing with the other for the army's scanty medical supplies. When Church did not fully comply with the regimental surgeons' requests for more adequate supplies, they accused him of deliberately withholding from them articles direly needed for the care of their sick. The Director-General in turn branded their demands as inordinate. Accusations were hurled back and forth. The altercations took on such dimensions that Washington, concluding that there was "either unpardonable abuse on one side, or an inexcusable neglect on the other", ordered the contending parties to appear before military courts of inquiry[3]. The honeymoon, if there had been one, had lasted little more than a month.

The courts' hearings were held in rapid succession. The final hearing, cryptically postponed "until further orders . . . on account of the indisposition of Dr. Church", was never held. The Director-General had been placed under arrest! A Council of War, presided over by the Commander-in-Chief, found him guilty of holding criminal correspondence with the enemy. The army and country were stunned. In an official communication Washington informed the Congress of what had transpired[4]. "A painful, though necessary duty", he called it.

A letter, in cipher, addressed to a British officer in Boston (then within the enemy's lines), had been intercepted. The messenger, who turned out to be Church's mistress, had steadfastly refused to disclose the identity of the writer. Under "threat and persuasion" she had finally broken down and had named Dr. Church as its author. Church was immediately apprehended. He did not deny having written the letter, but he assured his interrogators that it contained nothing criminal. When deciphered it was found to be a queerly garbled, apparently innocuous, document. Church's papers, which had been seized at the time of his arrest, contained, as far as could be seen, nothing incriminating. However, there was a strong suspicion that a confidant of Church's had had access to them prior to their seizure. In view of the importance of the entire matter, the Council of War was turning it over to the Congress for further disposition. In the interim, Church was being held incommunicado.

On October 27th, Church was brought before the bar of the Massachusetts House of Representatives[5]. In his personally conducted, skillful defense (he had been refused counsel), he maintained that he had attempted to contact the British for the purpose of bringing about a termination of hostilities. Despite his eloquence he failed to convince the legislators of the purity of his motives. He was found guilty by them of having endeavored to carry on a "highly criminal and dangerous" correspondence with the enemy and was sentenced to solitary confinement, "without the use of pen, ink, and paper", and no one was to be permitted to converse with him except "in the presence and hearing of a Magistrate of the Town, or the Sheriff of the County . . . and in the English language".

Under the rigors of his imprisonment in the jail at Norwich, his health failed and after a year he was released under high bail. Finally, he was given permission to leave the country. The ship on which he sailed for the West Indies was lost at sea. He was never heard of again.

Immediately after Church's ignominious dismissal, the Congress approached Dr. John Morgan, one of America's most distinguished physicians, with the request that he take over the vacated post. Unhesitatingly, Morgan followed the call of his country. Little did he foresee how

tragically his decision to serve was to influence the future course of his life.

Morgan had an enviable record. After serving a medical apprenticeship in his native Philadelphia, he had gone abroad to complete his medical education. At Edinburgh, the foremost English-speaking medical school of the day, he had received the university's coveted medical degree. In London he had sat at the feet of the famous Doctors Hunter and had trained under the renowned Dr. John Fothergill. At Paris and Padua he had rounded out his medical studies. Not yet thirty, he had received the distinction of being elected a Fellow of the Royal Society, a Licentiate of the Royal Colleges of Edinburgh and London, a member of the Académie Royale de Chirurgie of Paris and of the Society of Belles-Lettres of Rome.

On his return to Philadelphia, in 1765, he became the prime mover in the founding of the first medical school in America, and in the same year he was appointed to the new institution's professorship of the "Theory and Practice of Physic". Within a few years he was one of Philadelphia's most sought-after doctors.

When Morgan reported to General Washington for duty at Cambridge, in the middle of October, he found the medical department in a state of turmoil and confusion, still shaken by the shock of the Church affair. With his customary energy and organizational talent, the new Director-General approached the many pressing problems that awaited him, foremost among them the procurement of medical supplies. Within a few weeks he was able to collect considerable quantities of hospital stores and some much-needed medicines. He also tackled the distasteful task of having to weed out those regimental surgeons who were unfit for medical duty with the army.

The quality of medical practice in colonial America varied tremendously. There were no established standards for the training of physicians, nor were there regulations for their licensure. Besides well-trained, highly qualified doctors, there was a large body of practitioners little better than quacks.

To separate the wheat from the chaff, the Massachusetts Provincial Congress had ruled in the early weeks of the war that all physicians were

to be examined by a committee of doctors before being commissioned as medical officers[6]. The examinations were very exacting. One of the candidates, the story goes, who had been "agitated into a state of perspiration", was asked to discuss measures for the treatment of rheumatism. Among others he proposed bringing the patient into a sweat. Asked how he would effect this in his patient, he said, after some hesitation, that he would "have him examined by a medical committee" [7].

During the chaotic weeks of Church's directorship the examinations had been discontinued. Morgan's insistence that they again be taken up met with the vehement resistance of the regimental surgeons, who did everything, from feigning illness to soliciting the intervention of their sponsors, the regimental commanders, to evade them. Morgan was soon as unpopular with them as Church had been.

Health conditions in the American encampment before Boston had generally been good. There had occurred, as was to be expected, cases of smallpox, dysentery and typhus, but there had been no major outbreaks of these dreaded diseases. The troops operating against Canada at this period were less fortunate. For them these maladies, especially smallpox, became more deadly than the weapons of the enemy. "The smallpox is ten times more terrible than the British, Canadians and Indians together", wrote John Adams.

The ill-fated expeditions against Quebec and Montreal had been hastily conceived and launched without sufficient medical, or other, preparation. Too few doctors were assigned to the army and they had virtually no medical supplies. From Fort George, Dr. Jonathan Potts reported that the distressed situation of the sick was "not to be described". He had under his care more than one thousand patients, crowded into sheds. To attend this large number there were, besides himself, only four senior physicians and four mates, and between them they had not a grain of medicine.

A young regimental surgeon who had been ordered to hospital duty in Isle-aux-Noix was appalled by the dreadful conditions there. "Language cannot describe nor imagination paint, the scenes of misery and distress the Soldiery endure", he notes in his Journal[8]. Their requests for help were "as little regarded as the singing of Crickets in a Summer's

evening". In one large barn, crowded with soldiers suffering from smallpox, he found many who could not see, speak or walk. Two had large maggots, an inch long, crawl out of their ears, and maggots were on almost every part of their body. "No mortal will ever believe what these suffered unless they were eye witnesses . . ." In a later entry he speaks of the sick who were "crowded into a dirty, lousy, stinking Hospital, enough to kill well men". "It made my heart ache to visit the Hospital, to see the Dysentery rage, with unabated fury among them; when I had not one article, calculated with their assistance . . ."

After the evacuation of Boston by the British on March 17, 1776, General Washington ordered Morgan to make preparations in anticipation of a campaign at New York. By the middle of the summer the Director-General had established several fairly well equipped hospitals there. The disastrous Battle of Long Island played havoc with his plans. The sick and wounded and the army's medical supplies had to be removed from the city to prevent them from falling into the hands of the enemy. Hastily, new installations were made ready in Westchester and on the New Jersey side of the Hudson. Morgan and his staff labored day and night. Especially the Director-General gave his all. He appeared to be everywhere at the same time. He personally picked the sites for the new hospitals; he himself supervised the evacuation of the patients; he directed the removal of the hospital stores; he spent many weary hours on horseback traveling back and forth; and, whenever he could, he attended the sick, dressing their wounds and giving orders for their care. Gradually he succeeded in bringing a semblance of order out of the chaos[9]. He all but collapsed under the strain.

His almost superhuman effort received but little recognition. He was even blamed by many for the inevitable disruption of orderly medical care. The injustice of the charge hurt him to the quick.

It is hard to visualize how scarce medical supplies were at this period. Fifteen regimental surgeons who had brought their own instruments had, among them, only four scalpels or knives for enlarging wounds, three pairs of forceps for extracting bullets, very few bandages and tourniquets, hardly any lint or tow and only two ounces of sponge. In the general confusion during the retreat from New York much equipment was lost. To one of his hospital surgeons, who had appealed for scalpels, Morgan wrote: "I send you two . . . if you want more, use a razor for an incision knife . . ." [10] Medicines could

only be had by buying them from private physicians who, understandably, were often reluctant to part with them. Morgan did not hesitate to apply pressure if necessary. "I must beg you will endeavour to procure me a list of the medicines for sale, belonging to Dr. Brownjohn; and the selling prices . . .", Morgan wrote to his above-mentioned aide, and ominously he added, "If Dr. Brownjohn is backwards to sell let me know; and I will take measures accordingly" [11].

During these trying weeks Morgan's implacable adversaries, the regimental surgeons, continued their attacks upon him with such vehemence that General Washington became convinced, as he informed Congress, that they were "aiming . . . to break up" the medical department. The Commander-in-Chief had harsh words for the regimental surgeons, many of whom, he said, were "very great rascals, countenancing the men in sham complaints to exempt them from duty, and often receiving bribes to certify indispositions with a view to procure discharges or furloughs". In "numberless instances" they had requisitioned medicines, hospital stores and other supplies in the "most profuse and extravagant manner for private purposes". To end the "constant bickering" between them and Morgan, Washington advised that they be made to "look up to the Director-General as a superior" [12].

Congress not only disregarded this recommendation, but it further undermined the authority of the Director-General by creating, without consulting Washington, an independent medical department for the army in New Jersey, to be headed by Dr. William Shippen, Jr. Morgan retained the title of Director-General, but he was given no authority over the new appointee, and his own jurisdiction was limited to the medical care of the troops on the east side of the Hudson.

It was an unheard-of step, which Morgan regarded as a demotion. Undoubtedly it was intended as such. Morgan's enemies had achieved their first visible success in their campaign to oust him.

The younger Shippen, who had apparently spearheaded the attack, was, like Morgan, a leading Philadelphia physician and Morgan's colleague at the Medical College. In him Morgan's detractors had obtained an influential, socially and politically well-connected ally. His father, the elder Dr. Shippen, was a member of Congress, as were his brothers-

in-law Richard Henry and Francis Lightfoot Lee, of Virginia. Shippen House, the family home, was a center of Philadelphia society.

During the following months Shippen, as we know from his correspondence, did not hesitate to utilize these connections to let his "friends in Congress" know that "neglect and iniquity in the medical department" had been responsible for the death of many more "brave Americans" than had been the "sword of the enemy". As to his own department, he was not ashamed to own "that he was conscious that it had many imperfections", but he "flattered" himself that none of them had "arisen from want of care and integrity in the director . . ."[13]

The underhanded attacks against Morgan continued through the fall. On January 9th, 1777, he was dismissed by Congress, without an explanation and without a hearing.

Morgan immediately requested an investigation of his conduct in office. He published an impassioned "Vindication of His Public Character in the Station of Director-General of the Military Hospitals, and Physician in Chief to the American Army"[9]. He virtually begged for the opportunity to appear before the Congress. For almost two years the legislators turned a deaf ear to his pleas. Finally, a congressional committee was appointed to hear him. On June 12th, 1779, the committee declared that ". . . Dr. John Morgan hath in the most satisfactory manner vindicated his conduct in every respect . . ."

The rehabilitation came too late. Morgan was a broken man. He retired more and more from public life and died a recluse, at the age of fifty-four. Dr. Benjamin Rush, who had been called to his bedside, recorded in his Commonplace Book, on October 15th, 1789, that he had found him "dead in a small hovel, surrounded with books and papers, and on a light dirty bed. He was attended only by a washerwoman, one of his tenants. . . . What a change from his former rank and prospects in Life! The man who once filled half the world with his name, had now scarcely friends enough left to bury him."[14]

Since the summer of 1776 there had been much sickness also among the main body of the American troops. The crowding of the soldiers in close quarters, especially in the hospitals, and the unsanitary conditions under which they lived contributed to a rapid, unrestrained spread of infectious and contagious diseases. At times, a fourth of the army

was on the sick list. A severe epidemic of "putrid diarrhea" (dysentery) broke out in the American encampment during the campaign for New York. "Multitudes melted away . . . from this miserable disease and died", wrote a contemporary army surgeon[15]. In the military hospitals at Princeton and Bethlehem, jail fever (typhus) took a dreadful toll, and the mortality among hospitalized soldiers in Philadelphia during the fall and winter of 1776-77 was so great that the dead could no longer be buried in single graves. Large square pits were dug in the potter's field and filled near to the top with coffins.

The suffering of the sick and dying was enhanced by the almost total lack of everything needed for their care. The doctors' frantic appeals to the authorities went mostly unheeded. "I have been incessantly making applications for these last twelve months to all the departments for supplies, but cannot procure any", wrote the commanding medical officer of the military hospital in Boston. "For some days [the sick] have not had an ounce of meat; not a stick of wood but what they have taken from the neighboring fences; for near a week not a vegetable; and scarcely any medicine for above a year"[16]. They would have perished but for the charitable donations of a few private individuals.

The morale of the hospitalized soldiers was at a low ebb. They disobeyed the surgeons and nurses, they quarreled and fought with one another, they went out as they pleased, they sold their arms, blankets and even their clothes to buy rum, and often they plundered the inhabitants in the neighborhood.

Everywhere it was the same melancholy story. The doctors were helpless. In bitter anger one of them thus gave vent to his feelings: ". . . Curse on him or them by whom [such] evil is produced. The vengeance of an offended Deity must overtake the miscreants sooner or later . . . I shall wait on his Excellency, the Commander-in-Chief, and represent our situation, but I am persuaded it can have little effect, for what can he do? He may refer the matter to Congress, they to the Medical Committee who would probably pow-wow over it for a while and no more heard of it. Thus we go before the wind . . ."[17]

At the beginning of April, 1777, three months after Morgan's dismissal, Shippen was appointed to the directorship of the recently reorganized medical department. Under the new set-up the Director-

General was given enhanced powers, the number of his aides was increased considerably, funds were more adequate and the regimental surgeons were, at last, placed under the Director-General's jurisdiction.

Despite such auspicious conditions Shippen, too, ended in failure. He possessed neither the earnestness of purpose nor the strength of character that would have been needed to cope successfully with the difficult situation under which he was called upon to direct the army's medical services. Vanity and the desire to supersede Morgan appear to have been the motives for his seeking the directorship of the medical department.

Among the doctors appointed by Congress to serve in important posts under Shippen there was young, capable and aspiring Dr. Benjamin Rush who, in later years, was to become the most famous American physician of his day. Now, at the age of thirty-one, he was a member of Congress and the chairman of its medical committee. In his desire to further serve the revolutionary cause he had volunteered for service in the army and had been appointed Surgeon General in the Middle Department. In this capacity he had seen duty in the military hospitals during the campaign for Philadelphia in the late summer of 1777, and he had become convinced that the system under which these hospitals were operated was in need of radical reorganization. He was also appalled by Shippen's handling of the affairs of the medical department. He believed the Director-General to be incompetent, negligent in performing his duties, and not above submitting incorrect reports on the number of sick and dead. He also suspected him of speculating in hospital stores.

In a letter to the Commander-in-Chief, Rush gave a detailed report on the abuses he had observed in the hospitals and he made suggestions on how they could be remedied[18]. He made no attack on the person of the Director-General. Rush's letter was submitted to Congress by Washington. Shippen and Rush were ordered to appear before a congressional committee, which absolved the Director-General. Rush thereupon handed in his resignation.

Conditions in the American military hospitals went from bad to worse. The desperate financial situation of the young republic made it nearly impossible to supply the hospitals with even the most necessary things for the care of the patients. Medicines, surgical instruments, often even food, were in shortest supply.

During these heavy and fateful years Morgan, who had lived in semi-retirement under the shadow of his humiliating dismissal, had never uttered in public a word against his successor. On June 15, 1779, three days after his vindication by Congress, he addressed a letter to John Jay, President of that body, charging Shippen with "Malpractice and Misconduct in Office", and offering to appear before a congressional committee to give evidence in support of his charges.

For many months, in spite of Morgan's further prodding, Congress did not move. The Director-General's important connections were apparently being brought into play. Pressure against Shippen became stronger. In March, 1780, the Director-General was arrested and brought before a court-martial. He was charged with selling and speculating in hospital stores, failure to keep proper accounts, neglect of his duties and other "Scandalous and infamous practices such as are unbecoming the Character of an Officer and Gentleman".

Rush, who testified against Shippen, accused him of negligence, of submitting to Congress reports of the sick and dead that were mostly false, of selling wine and sugar to tavernkeepers, of having "lived in a constant round of pleasure and dissipation". He further stated that in nine months' service he had never seen the Director-General inside a hospital.

The trial dragged on for several months. Shippen was formally acquitted on most counts. The court, however, found that he had speculated in and sold hospital stores, "that is, stores proper for hospitals . . . which conduct they consider highly improper, and justly reprehensible". Congress did not approve the court-martial's acquittal. Shippen was discharged from arrest but dismissed as Director-General. Reinstated a few months later, he shortly thereafter resigned "voluntarily". He had been given the opportunity to save face. Once again his powerful friends, it seems, had come to his assistance.

On January 17, 1781, Shippen's deputy, Dr. John Cochran, was appointed to succeed him. The new Director-General took over at a time when the medical department was on the point of disintegrating because of lack of funds. There was no money for the upkeep of the hospitals nor for the salaries of the army doctors. Many surgeons, Cochran informed the Chairman of the Medical Committee of Congress, had not received a shilling in nearly two years, and, appealing to a friend for help, another physician wrote: ". . . Joe and myself have

spent all our money, and fear, unless we can borrow, we shall starve; do pray prevent it by sending us cash. You may depend upon it, no Surgeons of the army can lend us a shilling".

Under such adversities and under the greatest personal risks (more army doctors died, in proportion to their numbers, than officers of the line) the medical men of the revolution carried on. Some may have been but fairly good doctors, some may not have been worthy of the trust placed in them, but the vast majority served their country faithfully according to their lights.

REFERENCES

1. Force, P. *Amer. Arch., 4th ser., 2*:1706.
2. *Journals of the Continental Congress*, July 27, 1775.
3. Force, P. *Amer. Arch., 4th ser., 3*:667.
4. Sparks, J. Boston, *Writings of George Washington 3*:115, 1834.
5. Force, P. *Amer. Arch., 4th ser., 3*:1479.
6. *Journals, Provincial Congr. Mass.*, Boston, 1838, p. 203.
7. Thacher, J. *A military journal during the American revolutionary war from 1775-1783.* Boston, Richardson and Lord, 1823, p. 28.
8. *Journal of Lewis Beebe*, F. R. Kirkland, edit. Phila., 1935, pp. 11 and 26.
9. Morgan, J. *A vindication of his public character in the station of Director-General of the Military Hospitals, and Physician-in-chief to the American Army; Anno, 1776.* Boston, 1777.
10. Warren, E. *Life of John Warren.* Boston, Noyes, Holmes & Co., 1874, p. 99.
11. *Ibid.*, p. 110.
12. Force, P. *Amer. Arch., 5th ser., 2*:498.
13. Ibid., *5th ser., 3*:1259.
14. Rush, Benjamin. Entry in his Commonplace Book for October 15, 1789. In *Autobiography of Benjamin Rush*, George W. Corner, edit. Princeton Univ. Pr., 1948, p. 180.
15. Tilton, J. *Economical observations on military hospitals.* Wilmington, J. Wilson, 1813, p. 61.
16. Warren, E. *Ref. 10*, p. 194.
17. Norris, G. W. *Early history of medicine in Philadelphia.* Phila., 1886, p. 201.
18. *Letters of Benjamin Rush*, L. H. Butterfield, edit. Princeton Univ. Pr., 1951, p. 180.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting on January 28, 1960, at The New York Academy of Medicine

Studies on the Phagocytic Function of the Reticuloendothelial System

BARUJ BENACERRAF

Department of Pathology, New York University College of Medicine

A technique has been described to assay the phagocytic activity of the reticuloendothelial system (RES) in various animal species by measuring the rate of clearance from the blood of a colloidal carbon suspension of known particle size (250 Å), which is phagocytized with great efficiency[1] by the cells of the RES in contact with the blood. Under these experimental conditions about 90 per cent of the injected carbon is recovered from the Kupffer cells of the liver and the reticulum cells of the spleen. The blood concentration decreases as an exponential function of the time according to equation 1, $\frac{\text{Log } C_1 - \text{Log } C_2}{T_2 - T_1} = k$

where C_1 and C_2 are carbon concentrations at the times T_1 and T_2 respectively. The rate of clearance k has been called the phagocytic index and is a measure of the phagocytic activity of the RES if a sufficient dose of carbon is injected to challenge all the phagocytic cells with an excess of particles. In this dose range, the rate of clearance k has been found to be inversely proportional to the dose of carbon injected, D: $k \times D = \text{constant}$ (equation 2). This behavior, which expresses the saturating effect of the phagocytized particles on the RES, characterizes the kinetics of phagocytosis of homogeneous particulate suspensions by the cells of the RES in contact with the blood.

This technique has been extensively used to assay the phagocytic capacity of the RES in various pathologic processes studied in animals, such as experimental infections of mice with Salmonella, Bacillus Calmette Guérin (BCG) or virulent tubercle bacillus. It was found that the RES responded to these bacterial infections with an increased phagocytic activity, which could reach very high values in the case of infection with avirulent organisms such as BCG. This hyperactive phase was soon followed by a severe depression of the phagocytic function shortly before death in the case of infection with virulent organisms such as Salmonella enteritidis[2].

With Drs. Old and Clarke the response of the RES to the implantation of transplantable tumors was investigated by the same methods.[3]

Tumors which have been repeatedly transplanted, such as Sarcoma 180, Carcinoma 755, Ehrlich carcinoma ascites, and Sarcoma 180 ascites, induce characteristic alterations in reticuloendothelial activity. During the early phase of tumor development, clearance rates are maximally elevated and remain increased throughout the period of rapid tumor growth. With progressive deterioration of the tumor-bearing host, reticuloendothelial activity returns to normal or below normal levels. A slight elevation in clearance rates has been observed during the growth of spontaneous mammary tumors in Swiss mice. Striking reticuloendothelial hyperplasia, following a brief phase of depressed carbon clearance, accompanies development of a reticulum cell leukemia induced by the Friend virus.

In addition, the effect of treatment with agents such as zymosan, BCG, and other products of microorganisms on the growth and lethality of various experimental tumors has been investigated. These agents, in addition to their ability to induce reticuloendothelial hyperplasia, enhance the capacity of the host to produce antibody and decrease host susceptibility to bacterial challenge. Swiss mice, infected with BCG or treated with zymosan, have been found protected against challenge with Sarcoma 180. Survival time is increased twofold in BCG-infected hosts inoculated with Ehrlich ascites.

REFERENCES

1. Benacerraf, B., Biozzi, G., Halpern, B. N. and Stiffel, C. *Physiopathology of the RES (Symposium)*. Oxford, Blackwell Sci. Publ. Ltd., 1957.
2. Biozzi, G., Halpern, B. N., Benacerraf, B. and Stiffel, C. Phagocytic activity of the reticuloendothelial system in experimental infections. In *Symposium*, ref. 1, p. 204.
3. Old, L. J., Clarke, D. A., Benacerraf, B. and Goldsmith, M. Reticulo-endothelial system and the neoplastic process. *Ann. N. Y. Acad. Sci.*, 1960. In press.

DISCUSSION

TIBOR BARKA: The topic of Dr. Benacerraf's excellent lecture, quantitation of the activity of RES, encourages me to bring to your attention some of our observations on the acid phosphatase activity of RE cells. Using a modified azo-dye method, we found that the RE cells (Kupffer cells of liver, reticular cells and macrophages of spleen, thymus and lymph node) contain high acid phosphatase activity, and they are characteristically stained by this technique. The acid phosphatase activity is localized in the form of granules, which store vital dyes also. These granular structures are probably identical with the lysosomes, as suggested by Novikoff. Following up the changes of acid phosphatase activity chemically and histochemically in different conditions known to influence the activity of the RES (injections of vital dyes, Thorotrast, typhoid vaccine, serum), we came to the conclusion that the measurement of acid phosphatase activity, especially in the spleen, thymus and lymph node, can be used as a quantitative parameter to characterize the activity of the RES in various organs.

BARUJ BENACERRAF: I think this is a nice presentation by Dr. Barka of a beautiful observation. In our laboratory Drs. Thorbecke and Old made a similar study where they also found a high level of acid phosphatase activity in the macrophage elements of the liver. They correlated these observations with carbon clearance studies in various experimental conditions such as BCG infection and tumors.

Ischemic Infarction and Swelling in the Rat Brain

SEYMOUR LEVINE

Department of Pathology, St. Francis Hospital, Jersey City, N. J.

Bilateral carotid artery ligation was performed on 200 rats, of which 139 died during the first two days with massive cerebral infarction. Gross and microscopic study of the entire brain within the intact (decalcified) skull revealed anatomic evidences of brain swelling analogous to those familiar from human autopsy material. There were curved grooves on the posterior aspects of the cerebral hemispheres due to pressure of the swollen infarcted forebrain against the rigid bony and dural tentorium, with herniation of brain substance around the tentorial edge. The medial cortices of the two hemispheres were closely apposed against each other, thus obliterating the median longitudinal fissure. The pineal was compressed into a triangular shape. The tectum of the midbrain was narrowed. The basilar and posterior communicating arteries had indented the brain substance.

Focal ischemic lesions were found in only 24 of the 61 rats that died or were sacrificed two to six days after surgery. The lesions

usually involved gray matter (cerebral cortex, corpus striatum, and hippocampus), but a few rats had white matter lesions (corpus callosum and callosal radiation). Most of the lesions were small. The paucity of lesions of intermediate severity suggested the operation of a vicious circle mechanism whereby lesions beyond a certain threshold of severity are associated with so much swelling as to compress vessels and cause more infarction, and so on, leading to early death with massive infarction.

It was found that the mortality following bilateral carotid ligation depended on the environmental temperature. In four experiments on warm, humid days, the mortality among control rats was 91 per cent, whereas the mortality among rats kept in an air-conditioned room was only 41 per cent. The control rats left in the warm, humid atmosphere had no change or an increase of body temperature, while those in the air-conditioned room had a fall of 1 to 4° in body temperature. The beneficial effect of air-conditioning may be due to increased resistance to cerebral anoxia consequent upon lowered body temperature. The detrimental effect of warm atmosphere may depend, in part, on a drop in blood pressure with resulting failure of collateral circulation.

These results indicate that bilateral carotid ligation in rats may prove to be a useful method for evaluating therapy for brain swelling associated with infarction. Cold injury has been used to produce brain swelling for therapeutic experiments on larger animals[1]; the lesions differed in being hemorrhagic and unilateral. Possible advantages of the method presented here include simplicity of the operative procedure, low cost of rats as test animals, and easy recognition of swelling by gross and microscopic criteria.

DISCUSSION

JAMES I. BERKMAN: May I ask a question, Dr. Zimmerman? Dr. Levine has been studiously avoiding the term cerebral edema in talking about brain swelling. Will he tell us why?

SEYMOUR LEVINE: As is well known, the terms edema and swelling are based on the premise of excess accumulation of fluid in the brain, which may be extracellular or intracellular. In view of the observations of Torack, Terry and Zimmerman[2], and others, that there is almost no interstitial or intercellular space in the rat brain, the distinction between these terms has now become questionable, and perhaps old-fashioned, so I avoided this problem. Obviously my experiments were in no way designed to shed any light on this problem, but I would refer you to the paper by Drs. Torack, Terry and Zimmerman.

HANS POPPER: Is the increase of the brain weight the result of imbibition of serum or of water? Do you find an increase of protein in the brain?

SEYMOUR LEVINE: I have not measured these things; I cannot give you any direct answer, but I think one can suspect there is an exudation of protein; increase of capillary permeability has been demonstrated repeatedly under similar circumstances. I am sure the vessels are necrotic, and I have no doubt there is an increase in protein as well as in water.

HANS POPPER: Your experiment is an excellent model to study experimentally the nature of the increased protein.

SEYMOUR LEVINE: I am sure what you said is correct; it is a very simple technique; nothing is involved but ligation of the carotids in the rat, and it is quite easy to recognize the swelling.

H. M. ZIMMERMAN: I take it we shall all go back and talk to our deans and hospital administrators about air-conditioning our offices!

REFERENCES

1. Raimondi, A. J., Clasen, R. A., Beattie, E. J. and Taylor, C. B. Effect of hypothermia and steroid therapy on experimental cerebral injury, *Surg. Gynec. Obstet. 108*:333-38, 1959.
2. Torack, R. M., Terry, R. D. and Zimmerman, H. M. Fine structure of cerebral fluid accumulation. I. Swelling secondary to cold injury, *Amer. J. Path. 35*:1135-47, 1959.

*The Effect of Parabiosis on the Development of Immunity to the Novikoff Hepatoma in Rats**

KURT LANGE, GERHARD TRESER, STEPHEN E. MCPHERSON AND EUGENE J. WENK

From the Department of Medicine, New York Medical College-Metropolitan Medical Center, New York City

Rats of the Sprague-Dawley strain and rats of the related Charles River strain (derived nine years ago from Sprague-Dawley rats) were joined in different combinations by a technique of parabiosis which did not create a common peritoneal cavity.

The Novikoff hepatoma, originally produced by injection of 4-dimethyl-amino-azobenzene (butter yellow) into Sprague-Dawley rats, was transplanted without difficulty into Sprague-Dawley rats but could not be carried in Charles River rats for more than five successive transplants.

The development of a tumor by inoculation of the secondary member of a parabiotic pair of Sprague-Dawley rats is not prevented by the successful implantation of a tumor in the primary member 11 days before.

The development of a tumor in the secondary member of parabiotic pairs of Charles River rats is not prevented by the successful implantation of a tumor in the primary partner six days before the secondary member is inoculated. It is prevented, however, in 9 out of 12 instances when the interval between the inoculation of the primary and the secondary partner is 11 days or more, thus permitting development of antibodies in the parabiotic pair.

If, in a combination of Charles River rats with Charles River rats, the primary partner is immune to the tumor, as in two out of 12 instances cited, the secondary member takes the tumor.

The development of a tumor in parabiotic pairs of Charles River rats with Sprague-Dawley rats is prevented by the successful implantation of tumor in the Sprague-Dawley partner 11 days prior to the implantation in Charles River rats. If the Sprague-Dawley partner did not take the tumor, the implantation took in the Charles River rats.

The development of a tumor in a parabiotic pair of Sprague-Dawley and Charles River rats was prevented in 10 out of 15 instances when the Charles River animal received the inoculation as the primary member. Subsequent tumor inoculations in the primary partner led to a rapid anaphylactic death in many of the pairs, while survivors showed necrosis of the parabiotic connection, an effect never encountered except in this instance. Four pairs in which the primary Charles River rat survived without take showed a take in Sprague-Dawley rats after subsequent inoculations when the parabiotic connection had become necrotic.

It is suggested that the Charles River rats form antibodies against the tissue of the related Sprague-Dawley strain, but that these antibodies are not directed against the tumor, but against the heterogenic Sprague-Dawley protein.

DISCUSSION

ALEX B. NOVIKOFF: I am pleased to see that this tumor is being used to such good advantage. I would like to ask Dr. Lange about spontaneous regression. This concerns the experiments in which the primary members of the parabiotic pairs were given intramuscular transplants. In our experience about 40 per cent of the animals

* Aided by Grant A-302 of the Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

with intramuscular tumor transplants show spontaneous regression. What was the incidence of such regression in your animals?

KURT LANGE: All of the primary members of the parabiotic pairs were injected intramuscularly with the tumor. We have not seen spontaneous regression, but this may very well be due to the fact that our animals were sacrificed within a short period of time, usually less than 20 days, so that they did not have much chance to show a regression.

MAX WACHSTEIN: Dr. Lange was talking about antibodies. Did you do any direct antibody studies?

KURT LANGE: Yes, we did. We used for this purpose the technique of fluorescein-labelled antibodies. While these experiments are not sufficiently advanced to make a definite statement, we can say that it appears that a gamma globulin of resistant Charles River rats acts as an antibody to the tumor, staining the tumor masses specifically.

HANS POPPER: What is the behavior of skin transplants under these circumstances?

KURT LANGE: I do not know. We have not tried to transplant skin from one parabiont to another between related strains. It would be necessary that the tissue graft takes initially in order to stimulate sufficient antibody formation for later rejection. If it does not take for technical reasons, the small amount of tissue implanted usually does not suffice to produce enough antibody formation to lead to a rejection of a later graft.

NEW YORK HEART ASSOCIATION

Scientific Session Held at The New York Academy of Medicine, April 20, 1960

ABSTRACTS OF PAPERS SUBMITTED FOR PRESENTATION

(Part I)

The Retention of Sodium by Previously Edematous Cardiacs (Abstract)*

HUGH J. CARROLL AND SAUL J. FARBER

Department of Medicine, New York University School of Medicine, and the Third Medical Division, Bellevue Hospital, New York.

Edematous cardiacs have an elevated total body sodium. This level falls when they become edema free, but in over half of the cases the ratio of body sodium to body weight and to total body water remains elevated. This study was undertaken to determine whether the body sodium content eventually returns to normal.

In 18 previously edematous cardiacs measurements were made of body weight, total body water (antipyrine space, A.S.), and total exchangeable sodium (Na 24 space, TENa). In seven patients, studies were repeated at intervals for periods of two to five months following compensation.

In 18 patients, the mean ratio of exchangeable sodium to body water (TENa/A.S.) was 98.3 mEq./Liter (normal, 81.3). The ratio of exchangeable sodium to body weight (TENa/Bwt.) was 52.7 mEq./Kg. (normal, 43.7). Three patients showed a fall in TENa over a period of months without a fall in body weight or body water. Their ratios of TENa/A.S. and TENa/Bwt returned to normal. Four patients showed no loss of excess body sodium during a similar period, their ratios remaining high.

There is evidence to suggest that this excess sodium may be bound in an osmotically inactive form in the body, and the nature of this binding is under study. The reason for the prolonged retention of sodium excess by some dry cardiacs, and not by others, remains to be determined.

* Presented at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

Cardiac Nucleotides and Derivatives in Acute and Chronic Ventricular Failure of the Dog Heart (Abstract)*

N. M. BUCKLEY AND K. K. TSUBOI, Ph.D.

Department of Physiology, Albert Einstein College of Medicine, and Department of Pediatrics, Cornell University Medical College, New York.

The myocardial nucleotides and their dephosphorylated derivatives were determined in samples from dog hearts subjected to acute or chronic hemodynamic overloading of the left ventricle.

Acute experiments consisted of evaluations of ventricular function in the three

* Presented at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

isolated dog hearts during a control period and after acute left ventricular failure had been produced. Chronic experiments consisted of weekly studies of ventricular function in four dogs in which aortic regurgitation was produced surgically, followed by evaluations in isolated heart preparations made from them after presumptive evidence of ventricular inadequacy had appeared. Control experiments consisted of two freshly excised dog hearts, and freshly made isolated heart preparations.

Muscle strips were excised from the ventricles of all hearts, homogenized and analyzed by ultraviolet absorption. Nucleotides and their derivatives were isolated and separated by chromatography and identified by their specific ultraviolet absorption characteristics.

The results include the amount and distribution of nucleotides, nucleosides and their bases in the right and left ventricles of each heart. There was no difference in amount or distribution of these compounds in right and left ventricle. There was a trend toward a smaller proportion of dephosphorylated derivatives in myocardium from acute or chronically failed hearts.

Direct Studies of the In Situ Specialized Conducting System (Abstract)*

PAUL F. CRANEFIELD, BRIAN F. HOFFMAN AND JACKSON H. STUCKEY

Departments of Physiology and Surgery, State University of New York Downstate Medical Center, Brooklyn, New York.

Contiguous bipolar electrodes have been attached to the endocardium of the canine heart during total cardiopulmonary by-pass by use of a pump-oxygenator. Electrodes have been positioned over the atrioventricular node, the bundle of His, the right or left bundle branches and the peripheral junctions of Purkinje fibers with ventricular muscle. Simultaneous records from these sites, and also from the right and left atria and right and left ventricles, have been recorded at the same time as a standard electrocardiogram.

Electrograms recorded in this manner have been employed to study the sequence of activation of the specialized conducting system during normal activity and during disturbances of rhythm and conduction. Records obtained permit subdivision of the P-R interval into intervals representing conduction from atrium to His bundle, His to bundle branches, bundle branches to peripheral Purkinje fibers and Purkinje fibers to ventricular muscle. Each of these sub-intervals can prolong independently of the others. Block in the specialized conducting system thus can be thought of as depending on several dissimilar elements arranged in series. Records from the specialized conducting system also indicate the site of initiation of activity in rhythms originating in areas other than the sinus node. The results of these studies are in disagreement with certain conclusions reached on the basis of interpretation of standard electrocardiograms.

* Presented at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

Purification and Properties of a Pituitary Component which Produces Lipemia in the Rabbit (Abstract)*

DANIEL RUDMAN, MARIO DI GIROLAMO, FLOYD SEIDMAN AND MARIA B. REID

Columbia University Research Service, Goldwater Memorial Hospital, and Department of Medicine, College of Physicians and Surgeons, Columbia University, New York.

Our previous studies showed that a single subcutaneous injection of an aqueous extract of anterior pituitary glands produces lipemia in the rabbit. Comparable lipemia is not produced by purified preparations of any of the recognized anterior pituitary hormones. Fractionation of the crude pituitary extract has now yielded a fraction (labelled "Fraction H") which produces lipemia in the rabbit. Bioassays have shown that Fraction H contains 0.07 per cent TSH, 0.002 per cent oxytocin, and no detectable amounts of the six other pituitary hormones.

The injection of as little as 0.25 mg. of Fraction H in the rabbit causes an increase in serum NEFA concentration from 200 μeq./L. to 2000 μeq./L. within one hour. This effect is not suppressed by intravenous infusion of glucose. The period of elevation of serum NEFA concentration varies from 2 to 24 hours, depending on dose of Fraction H. The rapid elevation of serum NEFA level is followed within 12 hours by a two- to five-fold increase in serum total lipid concentration. The increment of serum lipid has the following average composition: 85 per cent triglyceride, 10 per cent phospholipid, 5 per cent cholesterol.

Fraction H has the following properties: non-dialyzability; precipitation by 40 per cent $(NH_4)_2SO_4$ or 5 per cent $CHCl_3COOH$; solubility in the presence of high concentrations of ethanol or acetone; weak affinity for anion and cation exchange resins; stability of the biological activity to partial hydrolysis by HCl or pepsin; disappearance of the biological activity following partial hydrolysis by NaOH or trypsin. Inactivation by trypsin proves the presence of peptide bonds in the hormone molecule.

* Presented at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

Objective Evaluation of Myocardial Blood Supply In Vivo Through Observation of Acute Changes in Myocardial Temperature (Abstract)*

EDWARD I. GOLDSMITH AND HARRY J. MAYER, A.B.

Department of Surgery, The New York Hospital-Cornell Medical Center, New York.

These experiments were designed to estimate the hemic perfusion of a small peripheral mass of myocardium in living experimental animals with normal coronary arteries and following coronary arterial occlusions.

Modern instrumentation made it possible to observe and record very slight and transient temperature changes with a microprobe small enough to be embedded in the myocardium without significant damage to the tissue. A continuous record of the temperature of the surrounding cylindrical mass of myocardium was obtained. The temperature of the blood perfusing the myocardium was acutely reduced by the rapid injection of a standard dose of iced saline into the root of the aorta. The blood eventually reaching the myocardium was, thereby, "labeled" by its decreased temperature and was observed arriving and perfusing the region under study.

In normal animals, individually character-

* Presented at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

istic temperature curves were observed in the myocardium of the left and right ventricles following the injection of cold saline. In the left ventricular myocardium the temperature decline was abrupt, rapid and deep and recovery was prompt. In the right ventricular myocardium the fall occurred later, was not as sharp and recovery was slower. The order of magnitude of the decline was in the range of 0.5°C. The time response of the total event was in the range of two seconds.

In animals which had undergone slowly developing coronary occlusion and myocardial infarction, consistent deviations from the normal patterns were observed. In infarcted myocardium, temperature declines were slight or absent. In adjacent grossly normal areas of right ventricular myocardium, the temperature decline was more pronounced than normal and assumed the characteristics of normal left ventricular curves. These changes correlated with the state of vascularity, as interpreted by coronary arteriography and by microscopy.

These observations suggest the possibility of developing a quantitative method for measuring myocardial perfusion.

Collateral Pulmonary Blood Flow After Ligation of the Left Main Pulmonary Artery (Abstract)*

R. H. Goetz, M. Rohman, R. Dee, J. D. Haller and David State

Department of Surgery, Albert Einstein College of Medicine, New York.

There is considerable controversy concerning vasomotor control of the pulmonary circulation, the existence of reflex control being denied by some, whereas others feel that pulmonary vascular reflexes affect the clinical picture, limit surgical operability and influence postoperative results. It is well known that certain congenital cardiac and pulmonary lesions are associated with marked increase in bronchial flow, which may reach 25 per cent of the total cardiac output. Knowledge regarding the influence of increased bronchial circulation on pulmonary hemodynamics is still incomplete.

This report presents the results of experimental evaluation of factors modifying bronchial arterial flow in dogs using a technique of separate perfusion of the pulmonary and systemic circulations.

High bronchial flow rates were induced by ligation of the left main pulmonary artery, and development of increasing bronchial circulation was documented by special angiographic techniques, results of which will be shown.

It was demonstrated that, everything else being equal, the volume of bronchial flow varies directly with the systemic-pulmonary artery pressure gradient, below a certain level of which bronchial flow is abolished.

Bronchial arterial flow was demonstrated to be markedly increased with deflation, and decreased with inflation of the lungs.

Increasing the left auricular pressure resulted in a decrease in bronchial arterial flow, out of proportion to that expected from the decrease in systemic-pulmonary artery pressure gradient resulting from the increase in pulmonary artery pressure.

Alteration in temperature of the systemic and/or pulmonary perfusion affected bronchial arterial flow and the pulmonary flow-pressure relationship. The results will be presented.

It could be demonstrated that these and other procedures (including the effect of drugs) have a more pronounced effect on pulmonary hemodynamics in dogs with high bronchial flow than in normal animals; indeed, changes resulted from experimental procedures which were ineffectual in normal dogs.

The application of this data to certain thoracic and cardiovascular surgical problems will be discussed.

* Presented at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

Altered Relationship between the Pulmonary Resistance and the Lung Volume in Various Cardiopulmonary Disorders (Abstract)*

TSUNG O. CHENG

Cardiopulmonary Laboratory, the Brooklyn Hospital, and the Department of Medicine, State University of New York Downstate Medical Center, Brooklyn, New York.

That the pulmonary resistance varies with the state of inflation of the lungs has been previously reported (*J. appl. Physiol. 14:* 727, 1959). Pulmonary resistance was measured during both expiration and inspiration throughout the vital capacity, using the multiple interrupter technique originally described by Clements and Elam and modified by Cheng, Godfrey and Shepard. The pattern of pulmonary resistance versus lung volume varies very little in normal subjects. At and near maximal inspiration the resistance has a low value and remains low throughout most of the vital capacity until near the maximal expiratory level, where it changes rather abruptly to very high values. Inspiratory and expiratory resistances are practically identical in normal subjects, although the former is frequently lower than the latter, at a given lung volume. However, in patients with various cardiopulmonary disorders this normal relationship between the pulmonary resistance and the lung volume is altered. Furthermore, the changes in the pulmonary resistance during inspiration do not always follow those during expiration. The manner in which the pulmonary resistance-lung volume relationship is altered in asthma, emphysema, sarcoidosis, chronic pulmonary congestion and other cardiopulmonary disorders will be described. The type of alteration in the relationship between resistance and lung volume appears to depend on the pathophysiology of the various disorders.

* Submitted for presentation at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

Hyperguanidemia and Hypoglycemic Unresponsiveness in Renal Disease (Abstract)*

BURTON D. COHEN, NORTON SPRITZ, ALBERT L. RUBIN AND E. HUGH LUCKEY

Second Medical (Cornell) Division, Bellevue Hospital, and the Veterans Administration Hospital, New York.

Because of the occurrence of hypoglycemia in uremic patients during insulin and glucose treatment for hyperpotassemia, a group of 20 patients with renal disease was studied with the standard insulin tolerance test. These were matched with 19 comparably ill patients free of renal disease. Although the initial hypoglycemia was identical, a significantly delayed blood sugar recovery was noted in the kidney disease group. A similar group of 19 patients and 18 controls was given epinephrine followed by periodic blood sugar determinations. The response showed a diminished glycolysis in

* Submitted for presentation at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

the group with renal disease, suggesting a deficiency in liver glycogen storage. In addition, spontaneous hyperglycemia has been demonstrated in non-diabetics with renal disease. These paradoxical findings implicate an agent, accumulating in the presence of renal disease, which blocks hepatic glycogenesis. Plasma determinations of guanidine, methylguanidine, arginine, guanidinoacetic acid, creatine and creatinine revealed a significant elevation of the latter three in the patients with renal disease. The data support the contention that guanidinoacetic acid is a precursor of creatine and creatinine, and that guanidine and methylguanidine play no role in this metabolic pathway. The retained guanides, members of a group of substances known to be effective in reducing liver glycogen, may play a significant role in the abnormal carbohydrate metabolism demonstrated in renal disease.

Preferential and Active Transport of Linoleic Acid by Polymorphonuclear Leukocytes (Abstract)*

PETER ELSBACH

Department of Medicine, New York University School of Medicine, New York.

Previous experiments, using ^{14}C-1-acetate as an index of synthesis, have shown that polymorphonuclear leukocytes, obtained from rabbit peritoneal exudates, synthesize most fatty acids *in vitro*. However, little or no radioactivity was found associated with linoleic, linolenic and arachidonic acid, following recovery of individual fatty acids after gas-liquid chromatographic separation. Despite this evidence that these three essential fatty acids were not synthesized, it was found that the composition of the fatty acids remained constant in leukocytes actively metabolizing in a medium containing serum lipids (ascitic fluid). It was therefore concluded that intracellular levels are maintained by preferential transport and or relative exclusion from metabolic utilization.

The results of the present study indicate that preferential transport does take place and that the fatty acids accumulated are also metabolized.

Leukocytes were incubated in ascitic fluid containing either ^{14}C-1-linoleic acid (not synthesized by the leukocytes) or ^{14}C-1-palmitic acid (actively synthesized). Linoleic acid was reproducibly concentrated in the cell-lipids at a rapid rate, while palmitic acid was incorporated erratically and usually at a much slower rate.

The transport of both linoleic and palmitic acid into the cell was largely dependent upon anaerobic glycolysis, since iodoacetic acid and sodium fluoride inhibited uptake of labelled fatty acids, whereas dinitrophenol and KCN had little or no effect. No transport occurred during incubation at 4°C.

Metabolic utilization of accumulated ^{14}C-1-linoleic and ^{14}C-1-palmitic acid during incubation at 37°C was evidenced by appearance of increasing amounts of ^{14}C activity:

1) in CO_2 produced,
2) in water-washes of lipid extracts of successive samples of cells and medium,
3) in other fatty acids of lipids of cells and medium.

It is concluded that for maintenance of intracellular fatty acid composition, the leukocytes rely partly upon transport inward, and that in the case of linoleic acid, transport is the sole mechanism.

* Submitted for presentation at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

Long-Term Follow-Up of 130 Patients Who Have Undergone Mitral Valvular Commissurotomy (Abstract)*

DOROTHY ESTES, TOR RICHTER AND DANIEL L. LARSON

Department of Medicine, College of Physicians and Surgeons, Columbia University, New York.

There is considerable variation in the percentage of patients who are reported as improved following mitral valvular commissurotomy. In some of the larger studies published, the information obtained was based on incomplete patient evaluation and the period of follow-up was relatively short. The present study is an analysis of the functional and objective changes observed in 130 patients who were followed for periods of up to 8 years after operation. The patients were re-evaluated twice each year by the authors. At each visit each patient was questioned carefully about changes in symptoms, activities and limitations, medications required, and other major medical events that may have occurred. The physical findings were recorded after each visit. Electrocardiograms and chest x-rays were obtained yearly. By this method it was felt that the psychological factor in patients' complaints could be minimized and other factors that might affect the clinical state of the patient, apart from the effect of the mitral commissurotomy, could be recognized. The specific objectives of this study were: to determine the number of patients benefited by the operation; the effects of commissurotomy on the complications of rheumatic heart disease; to determine the mortality and causes of death in the operative and postoperative periods; and to determine criteria for selecting patients for mitral commissurotomy.

Forty-four per cent of the patients were classified as improved, 21 per cent showed no change, 11 per cent were made worse and 24 per cent have died. There has been a definite reduction in the incidence of hemoptysis, congestive heart failure and peripheral emboli. Atrial fibrillation has continued to appear in the postoperative period. Subacute bacterial endocarditis has occurred in high incidence in the immediate postoperative period. Of the 24 per cent who have died, 11 per cent died during the operative period, and 13 per cent during the period of follow-up. Major causes of death have been congestive heart failure and peripheral emboli. In this study, patients with severe congestive heart failure, calcification of the mitral valve and those falling into New York Heart Association Cardiac Classification IV usually failed to improve with the operation. A few of the "poor risk" patients have improved, however, and some of those with the most favorable outlook have been made worse by the operation. Our inability to identify accurately those who will benefit by the operation remains one of the major problems concerning mitral commissurotomy.

* Submitted for presentation at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

The Functional and Morphologic Effect of Left Ventriculotomy (Abstract)*

ALBERT FRANKEL, LAWRENCE I. ZAROFF AND IVAN D. BARONOFSKY

Department of Surgery, The Mount Sinai Hospital, New York.

With the advent of, and recent advances in intracardiac surgery, attention has been focused on broadening the surgical approaches to the heart. Though entry into the right ventricle has been fairly consistently successful, left ventriculotomy has been avoided clinically because of the fear of irreparably damaging this high pressure chamber. If this chamber could be safely attacked, one could anticipate a more satisfactory repair of certain intracardiac lesions, such as subaortic stenosis.

In order to investigate the healing and subsequent function of the left ventricle after surgical incision, the following study was undertaken. The left ventricle was incised in the intercoronary space in eight unselected mongrel dogs. The incisions averaged four centimeters in length. These were immediately repaired with continuous silk sutures. Neither inflow occlusion, hypothermia, nor cardiac bypass were employed. The incisions were allowed to heal for several months and then myocardial function curves were constructed for each left ventricle, plotting left ventricular work against left atrial filling pressure in seven of the eight animals. The animals were then sacrificed and their hearts examined grossly and microscopically.

All the ventriculotomy wounds healed with a dense fibrous scar without aneurysm formation and in only one was there evidence of suppuration around the sutures. Attempts to rupture the ventricle with an intraventricular balloon always resulted in rupture at high pressure at a site other than the scar. Functionally, these ventricles were generally unable to tolerate increased filling pressures and failed prematurely when compared with normal ventricles.

In summary, it is suggested that although healing is satisfactory from an anatomic point of view, the functional reserve of the left ventricle is impaired by left ventriculotomy.

* Submitted for presentation at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

Use of an Intracardiac Pacemaker in the Control of Heart Block (Abstract)*

SEYMOUR FURMAN, JOHN B. SCHWEDEL, GEORGE ROBINSON AND ELLIOTT S. HURWITT

Divisions of Surgery and Medicine, Montefiore Hospital, New York.

Heart block, either arteriosclerotic in origin or produced during repair of congenital cardiac defects, is a serious threat to life. A technique is available by which the heart may be caused to contract by application of an electric stimulus to the endocardial surface of the right ventricle. With endocardial stimulation, patients with heart block may be maintained for indefinite periods of time on an ambulatory, out-

* Submitted for presentation at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

patient basis. No increase in the resistance of the heart to stimulation has occurred to any of these patients.

Two patients with heart block following repair of congenital cardiac defects required use of endocardial stimulation. In one case, implanted myocardial wires were ineffective because of massive wound infection, and no other route of stimulation was possible. In the second patient, direct stimulation of the myocardium was continued until increasing resistance made further stimulation impossible. At that time endocardial stimulation was begun.

Fifteen patients in all have had intracardiac pacing. Of these, six are alive and well. Five are out-patients who are maintained with continuous stimulation of the heart. The other patient recovered sufficiently so that stimulation is no longer required.

Of the patients that died, none showed evidence of endocardial, myocardial or valvular damage caused by either the presence of the catheter or by electrical stimulation.

The Effect of Nitroglycerine on Coronary Vascular Resistance (Abstract)*

DOUGLAS M. GRIGGS, JR., RICHARD N. PIERSON, JR. AND ROBERT B. CASE

Department of Medicine, St. Luke's Hospital, New York.

The effect of nitroglycerine on coronary vascular resistance (CVR) was studied in the dog by fixing coronary flow and noting, as the response, a drop in coronary perfusion pressure. Blood was delivered by an occlusive pump from a femoral artery through a rotameter to the left main coronary artery via a Gregg cannula. Continuous recordings were made of the coronary flow, right atrial pressure, aortic pressure, and mean perfusion pressure proximal to the conorary cannula. CVR was expressed as pressure gradient/flow. A one ml. solution of nitroglycerine in saline or blood was injected into the perfusion circuit. A control sample without nitroglycerine was also injected. Delivery time from the site of injection to the coronary artery was known for the flow rate, so that the time of onset of response could be related to the presence of the agent. The results demonstrated a prompt fall in CVR when the drug reached the coronary circulation before a change in the heart rate or aortic pressure occurred. The percentage decrease in CVR was related to the dose administered as well as to the initial CVR. It was concluded that nitroglycerine produced a prompt, dose-related reduction in CVR.

* Submitted for presentation at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

THE NEW YORK ACADEMY OF MEDICINE

FIRST ANNUAL

CORRELATED CLINICAL SCIENCE COURSE

SEPTEMBER 6, 1960 THROUGH MAY 23, 1961

THIRTY-FIVE SESSIONS

TUESDAY EVENINGS 8 P.M. TO 10 P.M.

ADMISSION BY CARD ONLY

The Glorney Foundation has provided a grant in support of this initial course, accordingly **NO FEE** will be charged.

OBJECTIVES OF THE COURSE

The purpose of this course is to provide a basic review of selected aspects of the several human organ systems, with particular emphasis on their physiology, pharmacology and biochemistry as related to clinical disease. The course will consist of a series of seminars with active audience participation.

* * * * *

November 9, 1960 (Wednesday)

THROMBOSIS AND EMBOLISM

Irving S. Wright

URINARY SYSTEM

November 15, 1960

ANATOMY AND PHYSIOLOGY OF THE KIDNEY

Gerhard H. Giebisch, Richard H. Kessler

November 22, 1960

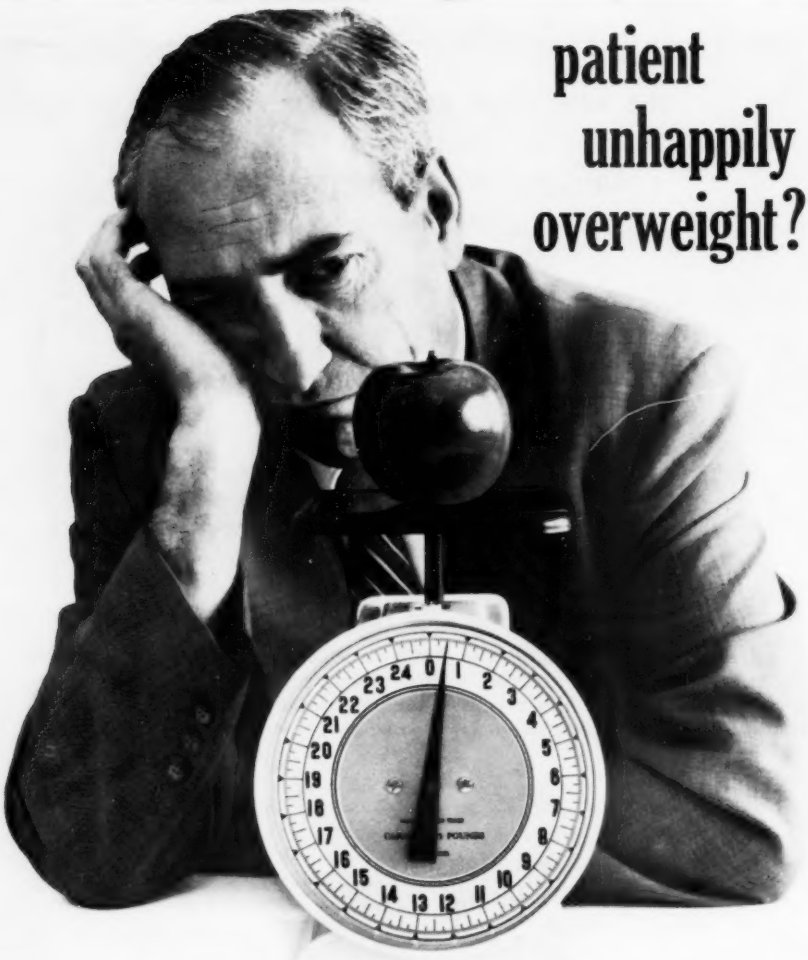
MEDICAL DISEASES OF THE KIDNEY

E. Lovell Becker

November 29, 1960

MECHANISMS OF INFECTION AND OBSTRUCTION OF THE URINARY TRACT

John H. McGovern



patient unhappily overweight?

minimize care and eliminate despair with

'METHEDRINE'®

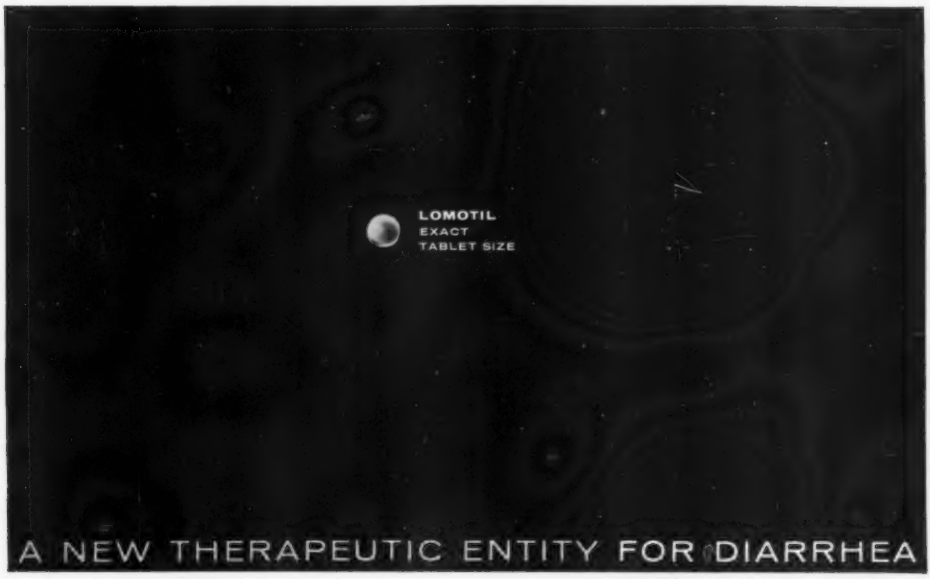
brand Methamphetamine Hydrochloride

Controls food craving, keeps the reducer happy—In obesity, "our drug of choice has been methedrine . . . because it produces the same central effect with about one-half the dose required with plain amphetamine, because the effect is more prolonged, and because undesirable peripheral effects are significantly minimized or entirely absent."[1] Literature available on request.

Supplied: Tablets 5 mg., scored. Bottles of 100 and 1000.

[1] Douglas, H. S.: West. J. Surg. 59:238 (May) 1951.

BURROUGHS WELLCOME & CO. (U. S. A.) INC., Tuckahoe, New York



A NEW THERAPEUTIC ENTITY FOR DIARRHEA

LOMOTIL®

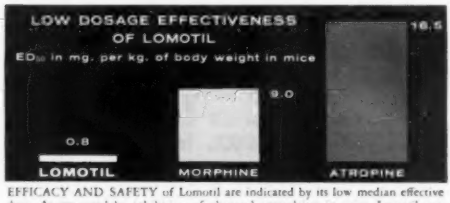
SELECTIVELY LOWERS PROPULSIVE MOTILITY

LOMOTIL represents a major advance over the opium derivatives in controlling the propulsive hypermotility occurring in diarrhea.

Precise quantitative pharmacologic studies demonstrate that Lomotil controls intestinal propulsion in approximately $\frac{1}{11}$ the dosage of morphine and $\frac{1}{20}$ the dosage of atropine and that therapeutic doses of Lomotil produce few or none of the diffuse untoward effects of these agents.

Clinical experience in 1,314 patients amply supports these findings. Even in such a severe test of antidiarrheal effectiveness as the colonic hyperactivity in patients with colectomy, Lomotil is effective in significantly slowing the fecal stream.

Whenever a paregoric-like action is indicated, Lomotil now offers positive antidiarrheal control . . . with safety and greater convenience. In addition, as a nonrefillable prescription product, Lomotil offers the physician full control of his patients' medication.



EFFICACY AND SAFETY of Lomotil are indicated by its low median effective dose. As measured by inhibition of charcoal propulsion in mice, Lomotil was effective in about $\frac{1}{11}$ the dosage of morphine hydrochloride and in about $\frac{1}{20}$ the dosage of atropine sulfate.

PRECAUTION: While it is necessary to classify Lomotil as a narcotic, no instance of addiction has been encountered in patients taking therapeutic doses. The abuse liability of Lomotil is comparable with that of codeine. Patients have taken therapeutic doses of Lomotil daily for as long as 300 days without showing withdrawal symptoms, even when challenged with nalorphine.

Recommended dosages should not be exceeded.

DOSAGE: The recommended initial dosage for adults is two tablets (5 mg.) three or four times daily, reduced to meet the requirements of each patient as soon as the diarrhea is controlled. Maintenance dosage may be as low as two tablets daily. Lomotil, brand of diphenoxylate hydrochloride with atropine sulfate, is supplied as unscored, uncoated white tablets of 2.5 mg., each containing 0.025 mg. ($\frac{1}{2400}$ gr.) of atropine sulfate to discourage deliberate overdosage.

Subject to Federal Narcotic Law.

Descriptive literature and directions for use available in Physicians' New Product Brochure No. 81 from

G. D. SEARLE & CO.
P.O. Box 5110, Chicago 80, Illinois
Research in the Service of Medicine

Now...
non-staining
water-soluble

ANTISEPTIC ANESTHETIC

RECTOCAINE® OINTMENT

- RECTOCAINE® OINTMENT is still the same recognized and accepted formula, now improved to meet the demands of the medical profession for RECTOCAINE® OINTMENT in a non-staining, water-soluble base, and in a convenient dispensing unit from which the label may be readily peeled off.
- RECTOCAINE® OINTMENT not only provides long acting antiseptic and anesthetic action for prompt and continued relief of pain, discomfort and itching in pruritis ani and hemorrhoids, but also in superficial burns and sunburns, cuts and bruises. Available in 1 oz. tubes (removable label) with rectal applicator, and 1 pound jars.
- RECTOCAINE® SUPPOSITORIES are available in boxes of 12.
- RECTOCAINE® INJECTION has been used for years to provide complete relief from pain before and after surgery for immediate ambulation and rapid return to normal occupational pursuits. Available in 5 cc. ampuls in boxes of 6, 25, and 100, and 20 cc. multiple dose vials.

C. F. KIRK COMPANY
PHARMACEUTICAL AND BIOLOGICAL LABORATORIES
521-523 WEST 23 STREET
NEW YORK 11, N. Y.

Through Physicians Only...

CONTACT LENS FITTING SERVICE

Only on prescription and under the supervision of the physician, Theo. E. Obrig, Inc. expertly fits contact lenses of all types. This has been a Theo. E. Obrig specialty for more than 25 years.

THEO. E. OBRIG, INC.
75 E. 55th St., N. Y. 22, N. Y., PL 8-0973

For acidosis due to anesthesia — edema

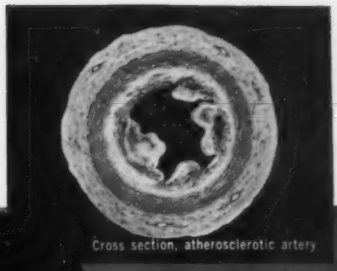
KALAK
Counter-Acts
ANTI-BIOTIC REACTIONS

. . . . KALAK is a non-laxative, alkaline diuretic buffer — side reactions from aureomycin — terramycin — sulfas — penicillin are reduced through the use of KALAK — KALAK contains only those salts *NORMALLY* present in plasma. . . . IT IS BASIC!

KALAK WATER CO.
of NEW YORK, Inc.
207 EAST 37TH STREET
New York 16, N. Y.

For acidosis due to nausea — in nephritis

outstanding nutritional research achievement



Cross section, atherosclerotic artery

to aid in the dietary control of serum cholesterol

MAZOLA®

MARGARINE

scientifically formulated with pure liquid **non-hydrogenated** MAZOLA Corn Oil.

MAZOLA Margarine is an economical tablespread and serves as a solid shortening, rich in linoleic acid and low in the more saturated fatty acids – making it an ideal dietary adjunct in the management of serum cholesterol. It contains 2 to 3 times as much linoleic acid as any other margarine in the grocery store, and 5 to 8 times as much as butter. It contains no dairy or animal fats, no coconut oil, and no cholesterol.

MAZOLA Margarine is indistinguishable from other quality margarines as to taste, aroma and handling characteristics. Thus, it can be part of the regular diet for the whole family, including the hypercholesterolemic patient. The major ingredient in MAZOLA Margarine – liquid MAZOLA Corn Oil–is NOT hydrogenated, thereby preserving its rich content of linoleates.

Two ounces or 56.8 Gm. (4 tablespoons) of MAZOLA Margarine supply:

Linoleic acid	12 Gm.
Oleic acid	23 Gm.
Saturated fatty acids	8 Gm.
Plant sterols (sitosterols)	215 mg.
Natural tocopherols	30 mg.
Vitamin A	1870 USP units
Vitamin D	250 USP units
Calories	415

Available in the refrigerator sections of grocery stores in the same general price range as other premium quality margarines, in 1-lb. packages (four ¼ lb. sticks).

Send for free booklet:
"Recent Advances in the Dietary Control of Hypercholesterolemia."

BEST FOODS • Division of Corn Products Co., NEW YORK 22, N. Y.

Herald Square, N. Y. *Roosevelt Field, Long Island*

Parkchester, Bronx *Jamaica, Queens*

White Plains, N. Y. *Flatbush, Brooklyn*

MACY'S PRESCRIPTION DEPARTMENT

Macy's is accurate. Our Prescription Department is a modern, sanitary laboratory, staffed by competent pharmacists. All of our completed prescriptions are carefully checked by supervising pharmacists. Our stock of ingredients is wide and reliable; it includes not only standard drugs, but also new and scarce products. And our prices are low.

No wonder so many physicians prefer Macy's Prescription Department.

Not Just "Milk" But . . .

WALKER-GORDON CERTIFIED MILKS

There are many reasons why thousands of discriminating families have been raised from infancy on Walker-Gordon Certified Milks. Among the reasons:

- *Super-Sanitary Production Methods.* From cow to bottle, milk is never exposed to air or human touch.
- *Cleanest.* Lowest bacteria count. Laboratory on the farm.
- *Freshest.* Bottled immediately after milking, usually delivered the following day. Keeps for weeks under normal refrigeration.
- *Uniform.* No variance in flavor or nutritional value, 365 days a year.

Guaranteed Free of Penicillin

Certified Milks available through Leading Milk Dealers: Raw, Pasteurized, Homogenized-Vitamin D, Skimmed, Acidophilus, Fresh Lo-Sodium. Write for complete information.

WALKER-GORDON CERTIFIED MILK FARM

Plainsboro, N.J. **SWinburne 9-1234**

NEW YORK: WAlker 5-7300 ★ **PHILA.: LOcust 7-2665**

The physician listens to a tense, nervous patient discuss her emotional problems. To help her, he prescribes Meprospan® (400 mg.), the only continuous-release form of meprobamate.

The patient takes one Meprospan-400 capsule at breakfast. She has been suffering from recurring states of anxiety which have no organic etiology.

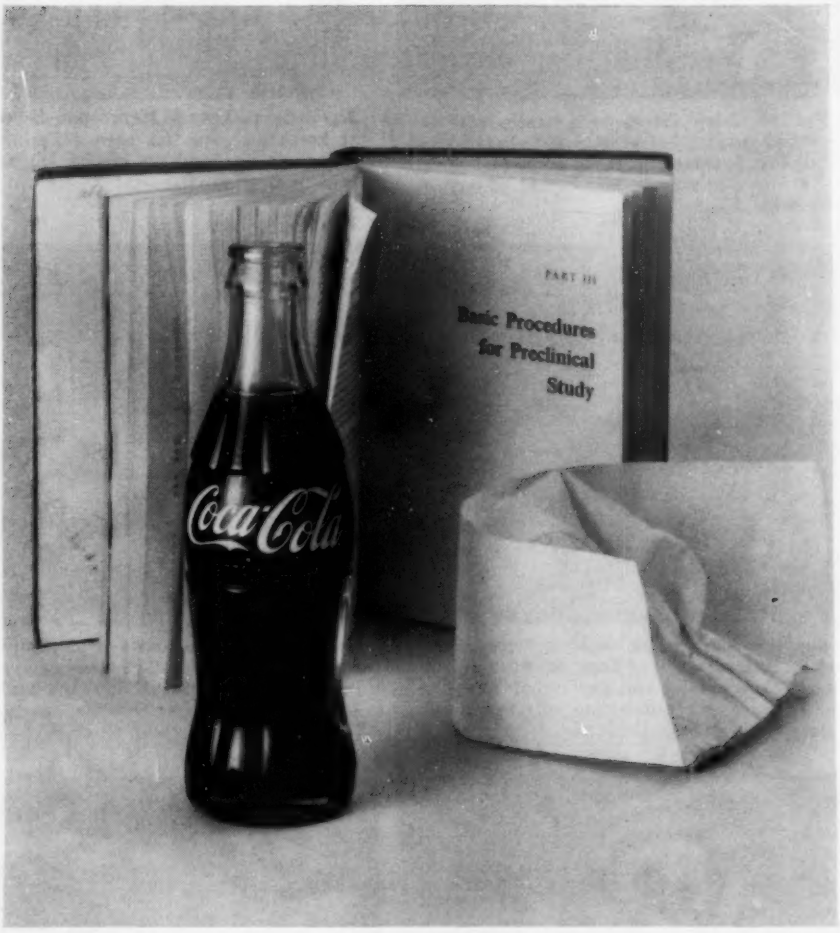
She stays calm while on Meprospan, even under the pressure of busy, crowded supermarket shopping. And she is not likely to experience any autonomic side reactions, sleepiness or other discomfort.

She takes another capsule of Meprospan-400 with her evening meal. She has enjoyed sustained tranquilization all day—and has had no between-dose letdowns. Now she can enjoy sustained tranquilization all through the night.

Relaxed, alert, attentive . . . she is able to listen carefully to P.T.A. proposals. For Meprospan does not affect either her mental or her physical efficiency.

Peacefully asleep . . . she rests, undisturbed by nervousness or tension. (Samples and literature on Meprospan available from Wallace Laboratories, Cranbury, N. J.)

CME-9064



When too many tasks seem to crowd the unyielding hours, a welcome "pause that refreshes" with ice-cold Coca-Cola often puts things into manageable order.

REFRESHES YOU BEST

DRINK Coca-Cola

— *PUBLISHED SYMPOSIA* —

SECTION ON MICROBIOLOGY

The New York Academy of Medicine

SYMPOSIUM NO. 1 Diagnosis of Viral and Rickettsial Infections Frank L. Horsfall, Jr., Editor [1949]	$3.75
SYMPOSIUM NO. 2 Evaluation of Chemotherapeutic Agents Colin M. MacLeod, Editor [1950]	$4.00
SYMPOSIUM NO. 3 The Pathogenesis and Pathology of Viral Diseases John G. Kidd, Editor [1950]	$5.00
SYMPOSIUM NO. 4* Parasitic Infections in Man Harry Most, Editor [1951]	$4.50
SYMPOSIUM NO. 5* Nature and Significance of the Antibody Response A. M. Pappenheimer, Jr., Editor [1953]	$5.00
SYMPOSIUM NO. 6 The Effect of ACTH and Cortisone upon Infection and Resistance Gregory Shwartzman, Editor [1953]	$5.00
SYMPOSIUM NO. 7 Streptococcal Infections Maclyn McCarty, Editor [1954]	$5.00
SYMPOSIUM NO. 8 Cellular Metabolism and Infections Efraim Racker, Editor [1954]	$4.80
SYMPOSIUM NO. 9 Cellular and Humoral Aspects of the Hypersensitive States H. Sherwood Lawrence, Editor [1959]	$18.00
SYMPOSIUM NO. 10 Viral Infections in Infancy and Childhood Harry M. Rose, Editor [1960]	$8.00

*Out of Print

Symposia Nos. 1-7 incl.—Published by Columbia University Press
Symposium No. 8—Published by Academic Press
Symposia Nos. 9 & 10—Published by Paul B. Hoeber, Inc.—
Medical Book Dept. of Harper & Bros.